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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Hudkins et al.

Serial No.: N/A

Group Art Unit: N/A

Filing Date: Herewith

Examiner: N/A

For: SELECTED DERIVATIVES OF K-252a

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**EXPRESS MAIL LABEL NO: EL568027858US
DATE OF DEPOSIT: November 8, 2000**

Box Patent Application
 Provisional Design

Assistant Commissioner for Patents
Washington DC 20231

Sir:

PATENT APPLICATION TRANSMITTAL LETTER

Transmitted herewith for filing, please find

☒ A Utility Patent Application under 37 C.F.R. 1.53(b).

It is a continuing application, as follows:

continuation divisional continuation-in-part of prior application number
08 / 867,084 .

A Provisional Patent Application under 37 C.F.R. 1.53(c).
 A Design Patent Application (submitted in duplicate).

Including the following:

- Provisional Application Cover Sheet.
- New or Revised Specification, including pages ____ to ____ containing:
 - Specification
 - Claims
 - Abstract
 - Substitute Specification, including Claims and Abstract.
- The present application is a continuation application of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Since none of those amendments incorporate new matter into the parent application, the present revised Specification also does not include new matter.
- The present application is a continuation application of Application No. _____ filed _____, which in turn is a continuation-in-part of Application No. _____ filed _____. The present application includes the Specification of the parent application which has been revised in accordance with the amendments filed in the parent application. Although the amendments in the parent C-I-P application may have incorporated new matter, since those are the only revisions included in the present application, the present application includes no new matter in relation to the parent application.
- A copy of earlier application Serial No. 08/867,084 Filed June 2, 1997, including Specification, Claims and Abstract (pages 1 - 143), to which no new matter has been added TOGETHER WITH a copy of the executed oath or declaration for such earlier application and all drawings and appendices. Such earlier application is hereby incorporated into the present application by reference.
- Please enter the following amendment to the Specification under the Cross-Reference to Related Applications section (or create such a section) : "This Application:
 - is a continuation of is a divisional of claims benefit of U.S. provisional Application Serial No. 08/867,084 filed June 2, 1997

- Signed Statement attached deleting inventor(s) named in the prior application.
- A Preliminary Amendment.
- _____ Sheets of Formal Informal Drawings.
- Petition to Accept Photographic Drawings.
 - Petition Fee
- An Copy of Executed Unexecuted Declaration or Oath and Power of Attorney.
- An Associate Power of Attorney.
- An Executed Copy of Executed Assignment of the Invention to _____
 - A Recordation Form Cover Sheet.
 - Recordation Fee - \$40.00.
- The prior application is assigned of record to Cephalon, Inc.
- Priority is claimed under 35 U.S.C. § 119 of Patent Application No. _____ filed _____ in _____ (country).
 - A Certified Copy of each of the above applications for which priority is claimed:
 - is enclosed.
 - has been filed in prior application Serial No. _____ filed _____.
- An Executed or Copy of Executed Earlier Statement Claiming Small Entity Status under 37 C.F.R. 1.9 and 1.27
 - is enclosed.
 - has been filed in prior application Serial No. _____ filed _____, said status is still proper and desired in present case.

Diskette Containing DNA/Amino Acid Sequence Information.

Statement to Support Submission of DNA/Amino Acid Sequence Information.

The computer readable form in this application _____, is identical with that filed in Application Serial Number _____, filed _____. In accordance with 37 CFR 1.821(e), please use the first-filed, last-filed or only computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification.

Information Disclosure Statement.

Attached Form 1449.

Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith.

A copy of Petition for Extension of Time as filed in the prior case.

Appended Material as follows: _____.

Return Receipt Postcard (should be specifically itemized).

Other as follows: _____ Petition for Extension of Time and Copy of Power of Attorney with Revocation and Certificate Under 37 CFR 3.73 (b) for U.S. Serial No. 08/867,084

_____.

FEE CALCULATION:

Cancel in this application original claims _____ of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	Fee	RATE	Fee
PROVISIONAL APPLICATION	\$75.00	\$	\$150.00	\$
DESIGN APPLICATION	\$160.00	\$	\$320.00	\$
UTILITY APPLICATIONS BASE FEE	\$355.00	\$	\$710.00	\$710.00
UTILITY APPLICATION; ALL CLAIMS CALCULATED AFTER ENTRY OF ALL AMENDMENTS				
	No. Filed	No. Extra		
TOTAL CLAIMS	22 - 20 =	2	\$9 each	\$18 each
INDEP. CLAIMS	4 - 3 =	1	\$40 each	\$80 each
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM	\$135		\$270	\$
ADDITIONAL FILING FEE		\$		\$
TOTAL FILING FEE DUE		\$		\$824.00

A Check is enclosed in the amount of \$ 824.00.

The Commissioner is authorized to charge payment of the following fees and to refund any overpayment associated with this communication or during the pendency of this application to deposit account 23-3050. This sheet is provided in duplicate.

The foregoing amount due.

Any additional filing fees required, including fees for the presentation of extra claims under 37 C.F.R. 1.16.

Any additional patent application processing fees under 37 C.F.R. 1.17 or 1.20(d).

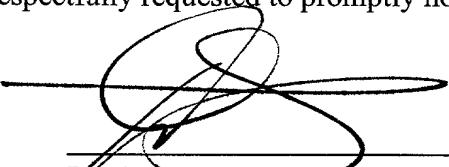
The issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance.

The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-

identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the United States Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: November 8, 2000



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SELECTED DERIVATIVES OF K-252a

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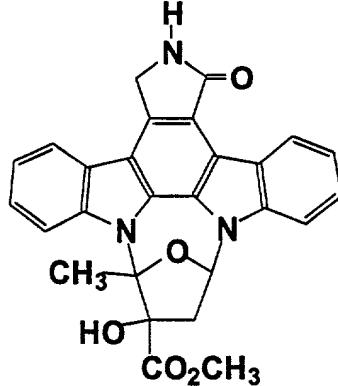
This application is a continuation-in-part of Serial No. 08/657,366, filed June 3, 1996.

FIELD OF INVENTION

This invention features selected ring-substituted derivatives of K-252a and their use for
10 treatment of neurological disorders.

BACKGROUND OF THE INVENTION

K-252a is a compound having an indolocarbazole skeleton represented by the following
15 formula [Japanese Published Unexamined Patent Application No. 41489/85 (US No. 4555402)].



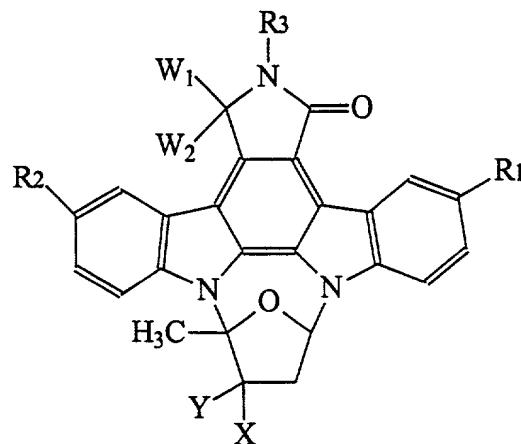
20 It has been reported that K-252a strongly inhibits protein kinase C (PKC) which plays a central role in regulating cell functions, and has various activities such as the action of inhibiting smooth muscle contraction (Jpn. J. Pharmacol. 43(suppl.): 284, 1987), the action of inhibiting serotonin secretion (Biochem. Biophys. Res. Commun., 144: 35, 1987), the action of inhibiting elongation of neuraxone (J. Neuroscience, 8: 715, 1988), the action of inhibiting histamine release
25 (Allergy, 43: 100, 1988), the action of inhibiting smooth muscle MLCK (J. Biol. Chem., 263: 6215, 1988), anti-inflammatory action (Acta Physiol. Hung., 80: 423, 1992), the activity of cell

survival (J. Neurochemistry, 64: 1502, 1995), etc. It has also been disclosed in Experimental Cell Research, 193: 175-182, 1991 that K-252a has the activity of inhibiting IL-2 production. Also the complete synthesis of K-252a has been achieved (J. Am. Chem. Soc., 117: 10413, 1995).

On the other hand, it has been disclosed that derivatives of K-252a have PKC inhibitory activity, the activity of inhibiting histamine release (Japanese Published Unexamined Patent Application No. 295588/88), antitumor activity [Japanese Published Unexamined Patent Application No. 168689/89 (US 4,877,776), WO 88/07045 (US 4,923,986)] etc., the action of increasing blood platelets [WO94/06799 (EP 630898A)], vasodepressor activity (Japanese Published Unexamined Patent Application No. 120388/87), the action of accelerating cholinergic neuron functions [WO 94/02488 (US 5,461,146)], curative effect on prostate cancer [WO 94/27982 (US 5,516,771)], etc.

SUMMARY OF THE INVENTION

The present invention relates to selected derivatives of K-252a represented by the general formula:



I

20

Constituent members are disclosed in detail, *infra*. Preferred methods for preparing these compounds and methods for using them are also disclosed.

DETAILED DESCRIPTION

I. Drawings

5 Figures 1 and 3 depict the structure of the substituted K-252a derivatives of the invention.
Figure 2 depicts the structure of K-252a.
Figure 4 is a schematic drawing showing the synthesis of a ring-substituted K-252a derivative from a ring-unsubstituted starting material.

10 Figure 5 is a schematic drawing showing the synthesis of a compound which contains at least one $-\text{CH}=\text{CH}(\text{CH}_2)_m\text{R}^{12}$ or $-\text{CH}=\text{CH}(\text{CH}_2)_n\text{R}^{18}$ ring substituent.

Figure 6 is a schematic drawing showing the synthesis of a compound which contains at least one $-\text{CH}=\text{CH}(\text{CH}_2)_n\text{R}^{13}$ or $-\text{CH}=\text{CH}(\text{CH}_2)_n\text{R}^{19}$ ring substituent.

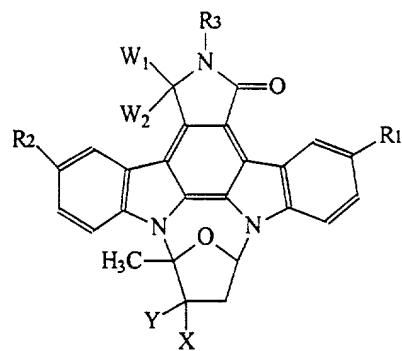
15 Figure 7 is a schematic drawing showing the synthesis of a compound which contains at least one $-(\text{CH}_2)_k\text{R}^7$ or $-(\text{CH}_2)_k\text{R}^{17}$ ring substituent.

Figure 8 is a schematic drawing showing the synthesis of a compound which contains a halogen or nitro ring substituent.

20 Figure 9 depicts the structures of certain known K-252a derivatives which are used as starting materials to prepare compounds of the invention.

II. Selected Ring-Substituted K-252a Derivatives

Disclosed herein are the selected ring-substituted derivatives of K-252a which are represented by the following formula:



1 wherein:

one of R^1 and R^2 is selected from the group consisting of:

a) $-\text{CO}(\text{CH}_2)_j\text{R}^4$, wherein j is 1 to 6, and R^4 is selected from the group consisting of:

- 1) hydrogen and a halogen;
- 2) $-\text{NR}^5\text{R}^6$, wherein R^5 and R^6 independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted aralkyl, unsubstituted aralkyl, lower alkylaminocarbonyl, or lower alkoxy carbonyl; or R^5 and R^6 are combined with a nitrogen atom to form a heterocyclic group;
- 3) N_3 ;
- 4) $-\text{SR}^{27}$, wherein R^{27} is selected from the group consisting of:
 - i) hydrogen;
 - ii) substituted lower alkyl;
 - iii) unsubstituted lower alkyl;
 - iv) substituted aryl;
 - v) unsubstituted aryl;
 - vi) substituted heteroaryl;
 - vii) unsubstituted heteroaryl;
 - viii) substituted aralkyl;
 - ix) unsubstituted aralkyl;
 - x) thiazolinyl;
 - xi) $-(\text{CH}_2)_a\text{CO}_2\text{R}^{28}$, wherein a is 1 or 2, and R^{28} is selected from the group consisting of: hydrogen and lower alkyl; and

xii) $-(CH_2)_aCONR^5R^6$; and

5) OR^{29} (wherein R^{29} is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, or COR^{30} (wherein R^{30} is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl));

5 b) $-CH(OH)(CH_2)_bR^{4A}$, wherein b is 1 to 6 and R^{4A} is hydrogen or the same as R^4 ;

c) $-(CH_2)_dCHR^{31}CO_2R^{32}$ wherein d is 0 to 5, R^{31} is hydrogen, $-CONR^5R^6$, or $-CO_2R^{33}$ (wherein R^{33} is hydrogen or lower alkyl), and R^{32} is hydrogen or lower alkyl;

d) $-(CH_2)_dCHR^{31}CONR^5R^6$;

e) $-(CH_2)_kR^7$ wherein k is 2 to 6, and R^7 is halogen, CO_2R^8 (wherein R^8 is

10 hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl), $CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^9 (wherein R^9 is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, substituted aryl, or unsubstituted aryl), SR^{27B} (wherein R^{27B} is the same as R^{27}), $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are the same as R^5 and R^6) or N_3 ;

15 f) $-CH=CH(CH_2)_mR^{12}$ wherein m is 0 to 4, and R^{12} is hydrogen, lower alkyl, CO_2R^{8A} (wherein R^{8A} is the same as R^8), $-CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^{9A} (wherein R^{9A} is the same as R^9), or $NR^{10A}R^{11A}$ (wherein R^{10A} and R^{11A} are the

20 same as R^5 and R^6);

g) $-CH=C(CO_2R^{33A})_2$, wherein R^{33A} is the same as R^{33} ;

h) $-C\equiv C(CH_2)_nR^{13}$, wherein n is 0 to 4, and R^{13} is the same as R^{12} ;

i) $-CH_2OR^{44}$, wherein R^{44} is substituted lower alkyl;

and the other of R^1 or R^2 is selected from the group consisting of

25 j) hydrogen, lower alkyl, halogen, acyl, nitro, $NR^{14}R^{15}$ (wherein R^{14} or R^{15} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

k) $-CH(SR^{34})_2$, wherein R^{34} is lower alkyl or alkylene;

l) $-CH_2R^{35}$, wherein R^{35} is OR^{36} (wherein R^{36} is tri-lower alkyl silyl in which the

30 three lower alkyl groups are the same or different, or is the same as R^{29}), or SR^{37} (wherein R^{37} is the same as R^{27});

m) $-\text{CO}(\text{CH}_2)_q\text{R}^{16}$, wherein q is 1 to 6, and R^{16} is the same as R^4 ;

n) $-\text{CH}(\text{OH})(\text{CH}_2)_e\text{R}^{38}$, wherein e is 1 to 6, and R^{38} is the same as R^{4A} ;

o) $-(\text{CH}_2)_f\text{CHR}^{39}\text{CO}_2\text{R}^{40}$, wherein f is 0 to 5, R^{39} is the same as R^{31} and R^{40} is the same as R^{32} ;

5 p) $-(\text{CH}_2)_r\text{R}^{17}$, wherein r is 2 to 6, and R^{17} is the same as R^7 ;

q) $-\text{CH}=\text{CH}(\text{CH}_2)_t\text{R}^{18}$, wherein t is 0 to 4, and R^{18} is the same as R^{12} ;

r) $-\text{CH}=\text{C}(\text{CO}_2\text{R}^{33B})_2$, wherein R^{33B} is the same as R^{33} ;

s) $-\text{C}\equiv\text{C}(\text{CH}_2)_u\text{R}^{19}$, wherein u is 0 to 4, and R^{19} is the same as R^{13});

R^3 is hydrogen, acyl, or lower alkyl;

10 X is selected from the group consisting of:

a) hydrogen;

b) formyl;

c) lower alkoxy carbonyl;

d) $-\text{CONR}^{20}\text{R}^{21}$, wherein:

15 R^{20} and R^{21} independently are:

hydrogen;

lower alkyl;

$-\text{CH}_2\text{R}^{22}$, wherein R^{22} is hydroxy, or

$-\text{NR}^{23}\text{R}^{24}$ (wherein R^{23} or R^{24} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, or the residue of an α -amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{23} and R^{24} are combined with a nitrogen atom to form a heterocyclic group); and

20 e) $-\text{CH}=\text{N}-\text{R}^{25}$, wherein R^{25} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

25 Y is hydroxy, lower alkoxy, aralkyloxy, or acyloxy; or

X and Y combined represent, $-\text{X}-\text{Y}-$, $=\text{O}$, $-\text{CH}_2\text{O}(\text{C}=\text{O})\text{O}-$, $-\text{CH}_2\text{OC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{NR}^{26}\text{C}(\text{=O})-$ (wherein R^{26} is hydrogen or lower alkyl), $-\text{CH}_2\text{NHC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{OS}(\text{=O})\text{O}-$, or $-\text{CH}_2\text{OC}(\text{CH}_3)_2\text{O}-$; and

W¹ and W² are hydrogen, or W¹ and W² together represent oxygen;

30 or a pharmaceutically acceptable salt thereof.

The compounds represented by formula (I) are hereinafter referred to as Compound (I), and the same applies to the compounds of other formula numbers.

In the definitions of the groups in formula (I), lower alkyl means a straight-chain or branched alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, 15 isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, 1-ethylpropyl and hexyl. The lower alkyl moiety of lower alkoxy, lower alkoxycarbonyl, lower alkylaminocarbonyl and tri-lower alkylsilyl has the same meaning as lower alkyl defined above. The acyl moiety of the acyl and the acyloxy groups means a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, such as 20 formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl and hexanoyl, an arylcarbonyl group described below, or a heteroarylcarbonyl group described below. The aryl moiety of the aryl, the arylcarbonyl and the arylaminocarbonyl groups means a group having 6 to 12 carbon atoms such as phenyl, biphenyl and naphthyl. The heteroaryl moiety of the heteroaryl and the heteroarylcarbonyl groups contain at least one hetero atom selected from O, S, and N, and include pyridyl, pyrimidyl, pyrrolyl, 25 furyl, thienyl, imidazolyl, triazolyl, tetrazolyl, quinolyl, isoquinolyl, benzimidazolyl, thiazolyl and benzothiazolyl. The aralkyl moiety of the aralkyl and the aralkyloxy groups means an aralkyl group having 7 to 15 carbon atoms, such as benzyl, phenethyl, benzhydryl and naphthylmethyl. The substituted lower alkyl group has 1 to 3 independently-selected substituents, such as hydroxy, lower 30 alkoxy, carboxyl, lower alkoxycarbonyl, nitro, amino, mono- or di-lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The lower alkyl moiety of the substituted lower alkyl, and the lower alkyl moiety of the lower alkoxy, the lower alkoxycarbonyl, and the mono- or di-lower alkylamino in the substituents of the substituted lower alkyl group have the same meaning as lower alkyl defined above. The substituted aryl, the substituted heteroaryl and the substituted aralkyl

groups each has 1 to 3 independently-selected substituents, such as lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino, mono- or di-lower alkylamino, and halogen. The lower alkyl moiety of the lower alkyl, the lower alkoxy, the lower alkoxycarbonyl, and the mono- or di-lower alkylamino groups among the substituents has the same meaning as lower alkyl defined above. The heterocyclic group formed with a nitrogen atom includes pyrrolidinyl, 5 piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl. The α -amino acid groups include glycine, alanine, proline, glutamic acid and lysine, which may be in the L-form, the D-form or in the form of a racemate. Halogen includes fluorine, chlorine, bromine and iodine.

10 Preferably, one of R^1 and R^2 is selected from the group consisting of $-(CH_2)_kR^7$, $-CH=CH(CH_2)_mR^{12}$, $-C\equiv C(CH_2)_nR^{13}$, $-CO(CH_2)_jSR^{27}$, and $-CH_2OR^{44}$ wherein R^{44} is methoxymethyl, ethoxymethyl, or methoxyethyl; and the other of R^1 and R^2 is selected from the group consisting of $-(CH_2)_lR^{17}$, $-CH=CH(CH_2)_lR^{18}$, $-C\equiv C(CH_2)_uR^{19}$, $NR^{14}R^{15}$, hydrogen, halogen, 15 nitro, $-CH_2O$ -(substituted or unsubstituted) lower alkyl, $-CO(CH_2)_qSR^{27}$, $-CH_2R^{35}$, $-CH_2OH$, and $-CH_2SR^{37}$ wherein R^{37} is selected from the group consisting of lower alkyl, pyridyl, and benzimidazole.

20 Preferably, R^{35} is OR^{36} wherein R^{36} , preferably, is selected from the group consisting of methoxymethyl, ethoxymethyl, and methoxyethyl.

25 Preferably, R^{27} is selected from the group consisting of substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, thiazole, and tetrazole.

Preferably, k and r , independently, are each 2, 3, or 4.

Preferably, j and q , independently, are 1 or 2.

30 Preferably, R^7 and R^{17} , independently, are selected from the group consisting of (1) CO_2R^8 and CO_2R^{8A} , where R^8 and R^{8A} , independently, are hydrogen, methyl, ethyl, or phenyl; (2) phenyl, pyridyl, imidazolyl, thiazolyl, or tetrazolyl; (3) OR^9 and OR^{9A} where R^9 and R^{9A} , independently, are hydrogen, methyl, ethyl, phenyl, or acyl; (4) SR^{27B} where R^{27B} is selected from the group consisting of unsubstituted lower alkyl, 2-thiazoline, and pyridyl; and (5) $NR^{10}R^{11}$ and $NR^{14}R^{15}$, where R^{10} , R^{11} , R^{14} , and R^{15} , independently, are selected from the group consisting of hydrogen, methyl, ethyl, phenyl, carbamoyl, and lower alkylaminocarbonyl.

Preferably, m , n , t and u , independently, are 0 or 1.

Preferably, R^{12} , R^{13} , R^{18} , and R^{19} , independently, are selected from the group consisting of hydrogen, methyl, ethyl, phenyl, pyridyl, imidazole, thiazole, tetrazole, CO_2R^8 , OR^9 , and $NR^{10}R^{11}$ where R^8 , R^9 , R^{10} , and R^{11} have the preferred values shown above.

Preferably, R^3 is hydrogen or acetyl, most preferably hydrogen.

5 Preferably, X is hydroxymethyl or lower alkoxy carbonyl with methoxycarbonyl being particularly preferred.

Preferably, Y is hydroxy or acetoxy, most preferably hydroxy.

Preferably, each W^1 and W^2 is hydrogen.

More preferred are the actual substituent values shown on the compounds in Table 1, with
10 Compounds 1-157 being especially preferred.

III. Utilities

The selected ring substituted K-252a derivatives have evidenced important functional
15 pharmacological activities which find utility in a variety of settings, including both research and therapeutic arenas. Generally, the activities of the compounds show positive effects on the function and/or survival of trophic factor responsive cells.

Effect on the function and/or survival of trophic factor responsive cells, e.g., cells of a neuronal lineage, can be established using any of the following assays: (1) cultured spinal cord
20 choline acetyltransferase ("ChAT") assay; or (2) cultured basal forebrain neuron ("BFN") ChAT activity assay.

As used herein, the term "effect" when used to modify the terms "function" and "survival" means a positive or negative alteration or change. An effect which is positive can be referred to herein as an "enhancement" or "enhancing" and an effect which is negative can be referred to herein
25 as "inhibition" or "inhibiting".

As used herein, the terms "enhance" or "enhancing" when used to modify the terms "function" or "survival" means that the presence of a substituted K-252a derivative has a positive effect on the function and/or survival of a trophic factor responsive cell compared with a cell in the absence of the derivative. For example, and not by way of limitation, with respect to the survival
30 of, e.g., a cholinergic neuron, the derivative would evidence enhancement of survival of a cholinergic neuronal population at risk of dying (due to, e.g., injury, a disease condition, a

degenerative condition or natural progression) when compared to a cholinergic neuronal population not presented with such derivative, if the treated population has a comparatively greater period of functionality than the non-treated population.

As used herein, "inhibit" and "inhibition" mean that a specified response of a designated material (e.g., enzymatic activity) is comparatively decreased in the presence of a substituted K-252a derivative..

As used herein the term "neuron," "cell of neuronal lineage" and "neuronal cell" includes, but is not limited to, a heterogeneous population of neuronal types having singular or multiple transmitters and/or singular or multiple functions; preferably, these are cholinergic and sensory neurons. As used herein, the phrase "cholinergic neuron" means neurons of the Central Nervous System (CNS) and Peripheral Nervous System (PNS) whose neurotransmitter is acetylcholine; exemplary are basal forebrain, striatal, and spinal cord neurons. As used herein, the phrase "sensory neuron" includes neurons responsive to environmental cues (e.g., temperature, movement) from, e.g., skin, muscle and joints; exemplary is a neuron from the dorsal root ganglion.

A "trophic factor-responsive cell," as defined herein, is a cell which includes a receptor to which a trophic factor can specifically bind; examples include neurons (e.g., cholinergic and sensory neurons) and non-neuronal cells (e.g., monocytes and neoplastic cells).

The disclosed aromatic ring substituted K-252a derivatives can be used to enhance the function and/or survival of cells of neuronal lineage. They can also be used to enhance the function and/or survival of cells of neuronal lineage in a mammal, e.g., a human. In these contexts, the derivatives can be utilized individually or with other derivatives, or in combination with other beneficial molecules which also evidence the ability to effect the function and/or survival of a designated cell.

A variety of neurological disorders are characterized by neuronal cells which are dying, injured, functionally comprised, undergoing axonal degeneration, at risk of dying, etc.. These disorders include, but are not limited to: Alzheimer's disease; motor neuron disorders (e.g. amyotrophic lateral sclerosis); Parkinson's; cerebrovascular disorders (e.g., stroke, ischaemia); Huntington's; AIDS dementia; epilepsy; multiple sclerosis; peripheral neuropathies (e.g., those affecting DRG neurons in chemotherapy-associated peripheral neuropathy) including diabetic

neuropathy; disorders induced by excitatory amino acids; disorders associated with concussive or penetrating injuries of the brain or spinal cord.

ChAT catalyzes the synthesis of the neurotransmitter acetylcholine, and it is considered an enzymatic marker for a functional cholinergic neuron. A functional neuron is also capable of survival. Neuron survival is assayed by quantitation of the specific uptake and enzymatic conversion of a dye (e.g., calcein AM) by living neurons.

Because of their varied utilities, the K-252a derivatives disclosed herein find utility in a variety of settings. The compounds can be used in the development of *in vitro* models of neuronal cell survival, function, identification, or for the screening of other synthetic compounds which have activities similar to that of the K-252a derivatives. The compounds can be utilized in a research environment to investigate, define and determine molecular targets associated with functional responses. For example, by radiolabelling a K-252a derivative associated with a specific cellular function (e.g., mitogenesis), the target entity to which the derivative binds can be identified, isolated, and purified for characterization.

The pharmaceutically acceptable salts of Compounds (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, organic amine addition salts, and amino acid addition salts. Examples of the acid addition salts are inorganic acid addition salts such as hydrochloride, sulfate and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, tartrate, citrate and lactate; examples of the metal salts are alkali metal salts such as lithium salt, sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminum salt, and zinc salt; examples of the ammonium salts are ammonium salt and tetramethylammonium salt; examples of the organic amine addition salts are salts with morpholine and piperidine; and examples of the amino acid addition salts are salts with glycine, phenylalanine, glutamic acid and lysine.

Compounds provided herein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. Such compositions can be prepared for use in parenteral administration, particularly in the form of liquid solutions or suspensions; or oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols; or dermally, via, for example, trans-dermal patches.

The composition can be conveniently administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as described in *Remington's Pharmaceutical Sciences* (Mack Pub. Co., Easton, PA, 1980). Formulations for parenteral administration may contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils and vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be useful excipients to control the release of the active compounds. Other potentially useful parenteral delivery systems for these active compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration may also include glycocholate for buccal administration, a salicylate for rectal administration, or citric acid for vaginal administration. Formulations for trans-dermal patches are preferably lipophilic emulsions.

The compounds of this invention can be employed as the sole active agent in a pharmaceutical composition. Alternatively, they can be used in combination with other active ingredients, e.g., other growth factors which facilitate neuronal survival or axonal regeneration in diseases or disorders.

Compound (I) and pharmaceutically acceptable salts thereof can be administered orally or non-orally, e.g., as an ointment or an injection. The concentrations of the compounds of this invention in a therapeutic composition can vary. The concentration will depend upon factors such as the total dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, the route of administration, the age, body weight and symptoms of a patient, etc.. The compounds of this invention typically are provided in an aqueous physiological buffer solution containing about 0.1 to 10% w/v compound for parenteral administration. Typical dose ranges are from about 1 μ g/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.01 mg/kg to 100 mg/kg of body weight per day, and preferably about 0.1 to 20 mg/kg once to four times per day. A preferred dosage of drug to be administered is likely to depend on variables such as the type and extent of progression of the disease or disorder, the overall health

status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration.

Compound (I) and pharmaceutically acceptable salts thereof can be administered as they are, or in the form of various pharmaceutical compositions, according to the pharmacological 5 activity and the purpose of administration. The pharmaceutical compositions in accordance with the present invention can be prepared by uniformly mixing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient, with a pharmaceutically acceptable carrier. The carrier may take a wide range of forms according to the forms of composition suitable for administration. It is desired that such pharmaceutical compositions are prepared in a unit dose 10 form suitable for oral or non-oral administration. The forms for non-oral administration include ointment and injection.

Tablets can be prepared using excipients such as lactose, glucose, sucrose, mannitol and methyl cellulose, disintegrating agents such as starch, sodium alginate, calcium carboxymethyl cellulose and crystalline cellulose, lubricants such as magnesium stearate and talc, binders such as 15 gelatin, polyvinyl alcohol, polyvinyl pyrrolidone, hydroxypropyl cellulose and methyl cellulose, surfactants such as sucrose fatty acid ester and sorbitol fatty acid ester, and the like in a conventional manner. It is preferred that each tablet contains 15-300 mg of the active ingredient.

Granules can be prepared using excipients such as lactose and sucrose, disintegrating agents such as starch, binders such as gelatin, and the like in a conventional manner. Powders can 20 be prepared using excipients such as lactose and mannitol, and the like in a conventional manner. Capsules can be prepared using gelatin, water, sucrose, gum arabic, sorbitol, glycerin, crystalline cellulose, magnesium stearate, talc, and the like in a conventional manner. It is preferred that each capsule contains 15-300 mg of the active ingredient.

Syrup preparations can be prepared using sugars such as sucrose, water, ethanol, and the 25 like in a conventional manner.

Ointment can be prepared using ointment bases such as vaseline, liquid paraffin, lanolin and macrogol, emulsifiers such as sodium lauryl lactate, benzalkonium chloride, sorbitan mono-fatty acid ester, sodium carboxymethyl cellulose and gum arabic, and the like in a conventional manner.

Injectable preparations can be prepared using solvents such as water, physiological saline, 30 vegetable oils (e.g., olive oil and peanut oil), ethyl oleate and propylene glycol, solubilizing agents

such as sodium benzoate, sodium salicylate and urethane, isotonicity agents such as sodium chloride and glucose, preservatives such as phenol, cresol, p-hydroxybenzoic ester and chlorobutanol, antioxidants such as ascorbic acid and sodium pyrosulfite, and the like in a conventional manner.

5 **IV. General Description of the Synthetic Processes**

The processes for preparing Compound (I) are described below.

Me, Et, Ph, Ac, Bn, Boc, and t-Bu in the structural formulae and tables represent methyl, ethyl, phenyl, acetyl, benzyl, tert-butoxycarbonyl, and tert-butyl, respectively.

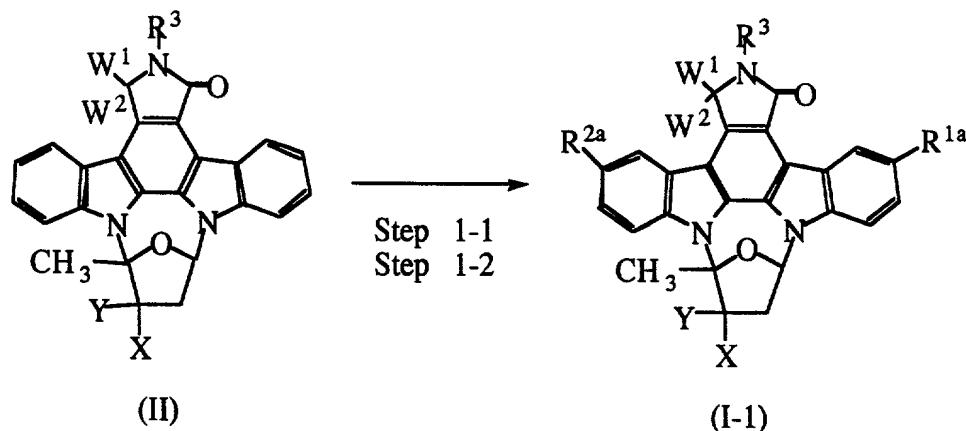
10 The compounds of the present invention can be usually obtained from optically active K-252a as the starting compound, but all possible stereoisomers and their mixtures are also within the scope of the present invention.

15 In the processes shown below, if the defined groups are converted under the conditions of the processes or are not suitable for carrying out the processes, the desired compounds can be obtained by employing means for introduction or elimination of protective groups conventionally used in organic synthetic chemistry. [See, e.g. T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons Inc. (1981)] Oxidation, reduction, addition, elimination, condensation, or hydrolysis, which is conventionally used in organic synthetic chemistry, may be carried out, and if necessary, the order of the reaction steps for the introduction of substituents, and 20 the like, may be varied. Further, conversion of the functional groups may be carried out more than one time.

Process 1

Compound (I-1), i.e., Compound (I) wherein at least one of R¹ and R² is -CO(CH₂)_jR⁴ (wherein j and R⁴ have the same significances as defined above), can be prepared according to the following reaction steps:

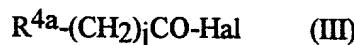
Fig. 4



5 [In the formulae, R^3 , W^1 , W^2 , X and Y have the same significances as defined above; and at least one of R^{1a} and R^{2a} is $-CO(CH_2)_jR^4$ (wherein j and R^4 have the same significances as defined above).]

Step 1-1:

10 Compound (I-1a), i.e., Compound (I-1) wherein R⁴ is halogen, can be obtained by subjecting Compound (II) which is a known compound described below to the Friedel-Crafts reaction with Compound (III) represented by formula (III):



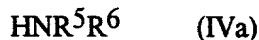
15 (wherein j has the same significance as defined above; R^{4a} is halogen as defined above; and Hal is chlorine or bromine) or acryloyl chloride in a solvent such as methylene chloride and chloroform in the presence of a Lewis acid such as aluminum chloride.

Compound (III) and the Lewis acid are respectively used in an amount of 1 to 20 equivalents based on Compound (II). The reaction is usually carried out at 0 to 80°C for 1 to 24 hours.

The starting Compound (II) can be prepared according to the processes disclosed in Japanese Published Unexamined Patent Applications Nos. 295588/88, 295589/88 and 807045/88.

Step 1-2:

Compound (I-1b), i.e., Compound (I-1) wherein R⁴ is NR⁵R⁶ (wherein R⁵ and R⁶ have the same significances as defined above), N₃, OR²⁹ (wherein R²⁹ has the same significance as defined above) or SR²⁷ (wherein R²⁷ has the same significance as defined above) can be obtained by subjecting Compound (I-1a) to reaction with a metallic salt of Compound (IVa) represented by formula (IVa):



(wherein R⁵ and R⁶ have the same significances as defined above), sodium azide, Compound (IVb)

represented by formula (IVb):



(wherein R²⁹ has the same significance as defined above), or Compound (IVc) represented by formula (IVc):

15



(wherein R²⁷ has the same significance as defined above) in a solvent such as methylene chloride, chloroform, dimethylsulfoxide or N,N-dimethylformamide, or reaction with Compound (IVa), (IVb) or (IVc) in the presence of a base such as potassium carbonate and triethylamine.

20

Compound (IVa), sodium azide, Compound (IVb), Compound (IVc) or a metallic salt thereof is used in an amount of 1 equivalent to excess amount based on Compound (I-1a), preferably 1 to 20 equivalents based on Compound (I-1a). A base is used in an amount of 1 to 20 equivalents. The reaction is usually carried out at 0 to 100°C for 1 to 24 hours.

25

Process 2

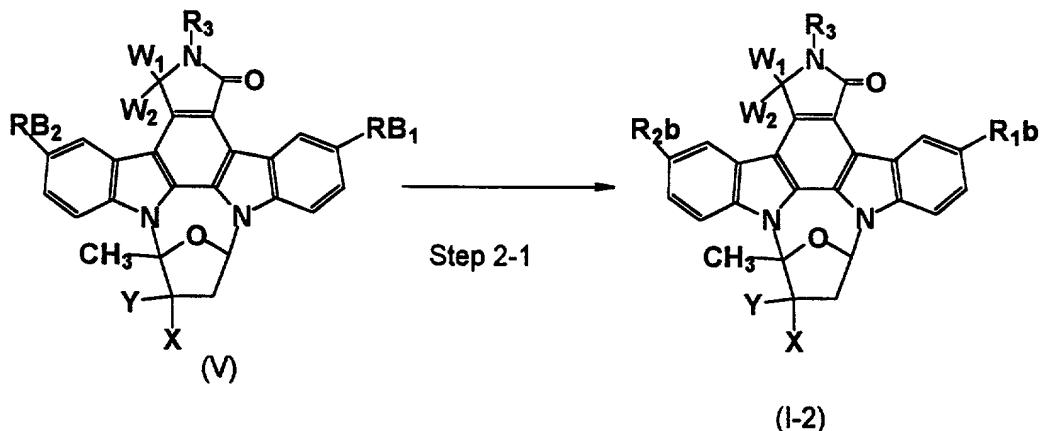
Compound (I-2), i.e., Compound (I) wherein at least one of R¹ and R² is -

CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above) or -

CH=C(CO₂R³³A)₂ (wherein R³³A has the same significance as defined above) can be prepared according to the following reaction steps:

30

Fig.5

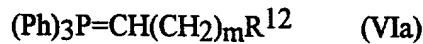


5

[In the formulae, R^3 , W^1 , W^2 , X and Y have the same significances as defined above; at least one of R^{B1} and R^{B2} is formyl, hydroxymethyl, halogen or $-C\equiv C(CH_2)_mR^{12}$ (wherein m and R^{12} have the same significances as defined above); and at least one of R^{1b} and R^{2b} is -
 10 $CH=CH(CH_2)_mR^{12}$ (wherein m and R^{12} have the same significances as defined above) or -
 $CH=C(CO_2R^{33A})_2$ (wherein R^{33A} has the same significance as defined above).]

Step 2-1:

Compound (I-2) can be obtained by subjecting Compound (Va) wherein at least one of R^{B1} and R^{B2} is formyl to reaction with Compound (VIa) represented by formula (VIa):



(wherein m and R^{12} have the same significances as defined above; and Ph is phenyl) in a solvent such as methylene chloride and chloroform. Alternatively, Compound (I-2) can be obtained by subjecting Compound (Va) to reaction with Compound (VIb) represented by formula (VIb):



(wherein m, R¹², Ph and Hal have the same significances as defined above) in a solvent such as methylene chloride and chloroform in the presence of a base such as potassium carbonate and

butyllithium. When a base which has poor solubility in the solvent, e.g. potassium carbonate, is used, the reaction is preferably carried out in the presence of a phase transfer catalyst such as 18-crown-6.

Compound (VIa), Compound (VIb) and the base are respectively used in an amount of 1 to 5 20 equivalents based on Compound (Va), and the phase transfer catalyst is used in an amount of 0.01 to 1 equivalent based on Compound (Va). The reaction is usually carried out at -10 to 100°C for 1 to 100 hours.

Compound (Va) can be prepared according to the process disclosed in Japanese Published Unexamined Patent Application No. 295588/88.

10

Step 2-2:

Compound (I-2) can be obtained by subjecting a phosphonium salt obtained from Compound (Vb) wherein at least one of R^{B1} and R^{B2} is hydroxymethyl and triphenylphosphine hydrobromide to reaction with Compound (VIc) represented by formula (VIc):

15

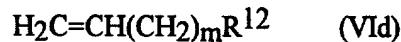


(wherein m and R^{12} have the same significances as defined above) in a solvent such as methylene chloride in the presence of a base such as potassium carbonate and butyllithium. Compound (Vb) can be prepared according to the processes disclosed in Japanese Published Unexamined Patent 20 Application No. 295588/88, WO94/02488, etc. When a base which has poor solubility in the solvent, e.g. potassium carbonate, is used, the reaction is preferably carried out in the presence of a phase transfer catalyst such as 18-crown-6.

Each of Compound (VIc) and the base is used in an amount of 1 to 20 equivalents based on the phosphonium salt (Vb), and the phase transfer catalyst is used in an amount of 0.01 to 1 25 equivalent based on the phosphonium salt (Vb). The reaction is usually carried out at -10 to 100°C for 1 to 100 hours.

Step 2-3:

Compound (I-2) can be obtained by subjecting Compound (Vc) wherein at least one of R^{B1} 30 and R^{B2} is halogen to Heck reaction with Compound (VId) represented by formula (VId):



(wherein m and R^{12} have the same significances as defined above) in a solvent such as N,N-dimethylformamide in the presence of a palladium compound such as palladium (II) acetate and

bistriphenylphosphine palladium (II) chloride, a phosphorus compound such as triphenylphosphine and tris(2-methylphenyl)phosphine and a base such as triethylamine.

Based on Compound (Vc), Compound (VId) is used in an amount of 1 to 40 equivalents, each of the palladium compound and phosphorus compound is used in an amount of 0.1 to 5 equivalents based on Compound (Vc), and the base is used in an amount of 1 to 500 equivalents. When the palladium compound used contains a phosphorus compound as a ligand as in the case of bis(triphenylphosphine)palladium (II) chloride, it is sometimes unnecessary to add the phosphorus compound. The reaction is usually carried out at 0 to 100°C for 1 to 10 hours.

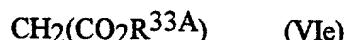
10 **Step 2-4:**

Compound (I-2) can be obtained by subjecting Compound (I-3) synthesized according to Step 3 described below to catalytic reduction in a solvent such as N,N-dimethylformamide in a stream of hydrogen in the presence of a reduction catalyst such as palladium/carbon.

15 The reduction catalyst is used in an amount of 10 to 100% by weight based on Compound (I-3). The reaction is usually carried out at 0 to 100°C for 1 to 72 hours.

20 **Step 2-5:**

Compound (I-2) can be obtained by subjecting Compound (Va) to reaction with a compound represented by formula (Vle):



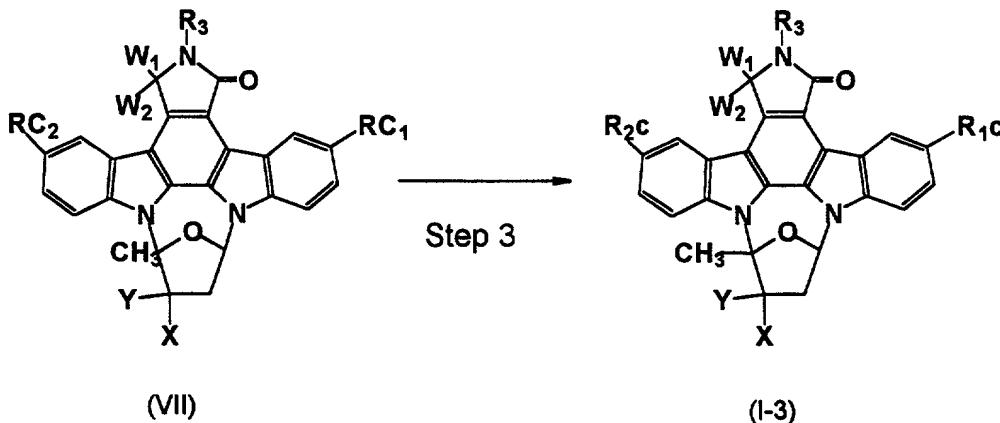
(wherein R^{33}A has the same significance as defined above) in a solvent such as chloroform and methylene chloride in the presence of a base such as piperidine.

25 Compound (Vle) is used in an amount of 1 to 40 equivalents based on Compound (Va), and the base is used in an amount of 0.1 equivalent based on Compound (Va) to an amount equivalent to the solvent. The reaction is usually carried out at 20 to 100°C for 1 to 24 hours.

Process 3

Compound (I-3), i.e., Compound (I) wherein at least one of R^1 and R^2 is $-\text{C}\equiv\text{C}(\text{CH}_2)_n\text{R}^{13}$ (wherein n and R^{13} have the same significances as defined above), can be prepared according to the following reaction steps:

Fig.6



5 [In the formulae, R^3 , W^1 , W^2 , X and Y have the same significances as defined above; at least one of RC_1 and RC_2 is iodine; and at least one of R^{1c} and R^{2c} is $-C\equiv C(CH_2)_nR^{13}$ (wherein n and R^{13} have the same significances as defined above).]

Step 3:

10 Compound (I-3) can be obtained by subjecting Compound (VII) to the Sonogashira reaction with Compound (VIII) represented by formula (VIII):



15 (wherein n and R^{13} have the same significances as defined above) in a solvent such as methylene chloride and chloroform in the presence of a copper compound such as cuprous iodide, a palladium compound such as palladium(II) acetate and bis(triphenylphosphine)palladium(II) chloride, a phosphorus compound such as triphenylphosphine, and a base such as diethylamine and triethylamine.

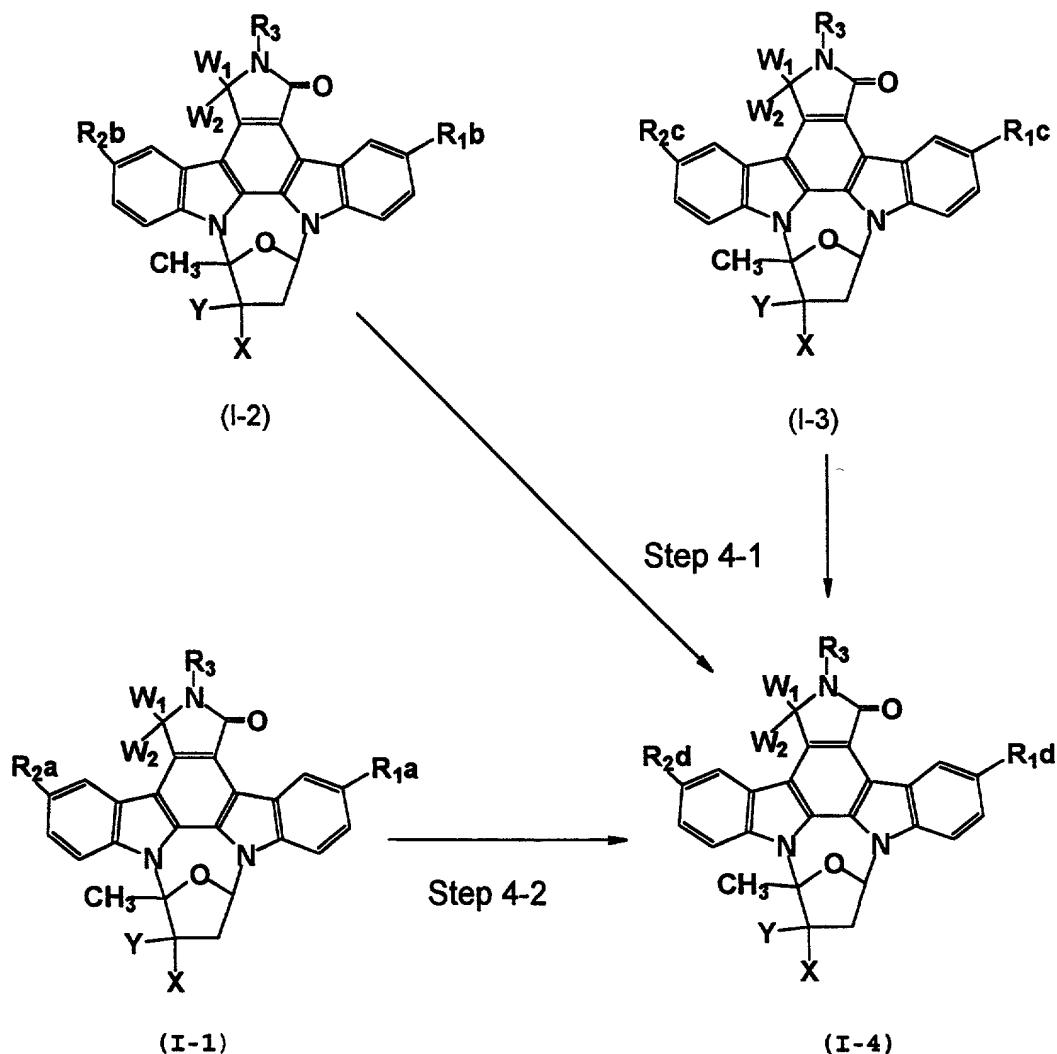
20 Compound (VIII) is used in an amount of 1 to 40 equivalents based on Compound (VII), the copper compound, the palladium compound and the phosphorus compound are respectively used in an amount of 0.1 to 5 equivalents, and the base is used in an amount of 1 to 500 equivalents. When the palladium compound contains the phosphorus compound as a ligand as in the case of bis(triphenylphosphine)palladium(II) chloride, it is not necessary to add the phosphorus compound. The reaction is usually carried out at 0 to 100°C for 1 to 10 hours.

Compound (VII) can be obtained by subjecting Compound (II) to reaction with iodine in a solvent such as methylene chloride/methanol mixture (4/1) in the presence of a mercury compound such as mercuric nitrate and mercuric chloride. The mercury compound and iodine are respectively used in an amount of 1 to 3 equivalents based on Compound (II). The reaction is usually carried out at 0 to 50°C for 1 to 24 hours.

Process 4

Compound (I-4), i.e., Compound (I) wherein at least one of R^1 and R^2 is $-(CH_2)_kR^7$ (wherein k and R^7 have the same significances as defined above) or $-CH_2CH(CO_2R^{33A})_2$ (wherein R^{33A} has the same significance as defined above), can be prepared according to the following reaction steps:

Fig.7



5

[In the formulae, R^{1b} , R^{2b} , R^{1c} , R^{2c} , R^3 , W^1 , W^2 , X and Y have the same significances as defined above; and at least one of R^{1d} and R^{2d} is $-(CH_2)_kR^7$ (wherein k and R^7 have the same significances as defined above) or $-CH_2CH(CO_2R^{33A})_2$ (wherein R^{33A} has the same significance as defined above).]

Step 4-1:

Compound (I-4) can be obtained by subjecting Compound (I-2) or Compound (I-3) to catalytic reduction in a solvent such as N,N-dimethylformamide in a stream of hydrogen in the presence of a reduction catalyst such as 10% palladium/carbon and platinum oxide.

5 The reduction catalyst is used in an amount of 10 to 100% (wt/wt) based on Compound (I-2) or Compound (I-3). The reaction is usually carried out at 0 to 100°C for 1 to 72 hours.

Step 4-2:

10 Compound (I-4) can be obtained by subjecting Compound (I-1) to reaction with alkylsilane such as ethylsilane in trifluoroacetic acid.

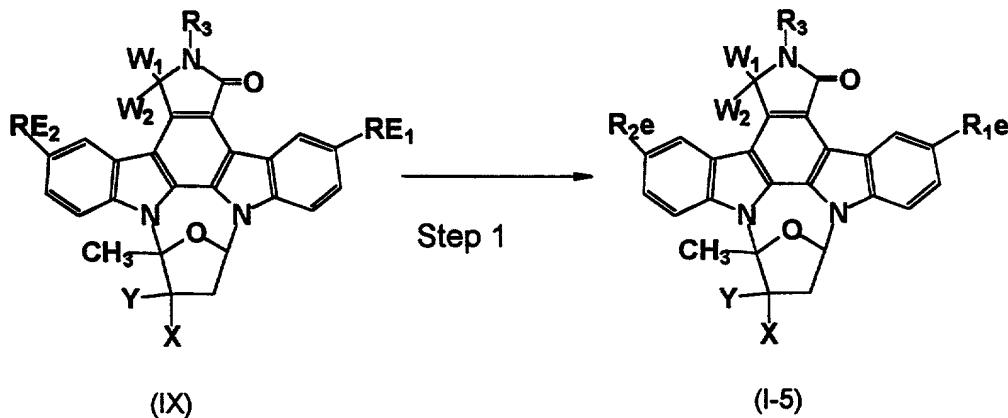
Trifluoroacetic acid is used in an amount equivalent to a solvent for Compound (I-1), and alkylsilane is used in an amount of 1 to 20 equivalents based on Compound (I-1). The reaction is usually carried out at -10 to 20°C for 1 to 24 hours.

15 **Process 5**

Compound (I-5), i.e., Compound (I) wherein either of R¹ and R² is halogen or nitro, can be prepared by subjecting Compound (IX) to the reactions in Steps 1-4 in Processes 1-4 described above. Compound (IX) can be prepared according to the processes described in Japanese Published Unexamined Patent Applications Nos. 120388/87 and 295588/88.

20

Fig.8



[In the formulae, R³, W¹, W², X and Y have the same significances as defined above; either of RE¹ and RE² is halogen or nitro, and the other is hydrogen; and either of R^{1e} and R^{2e} is halogen, nitro or amine, and the other is -CO(CH₂)_jR⁴ (wherein j and R⁴ have the same significances as defined above), -(CH₂)_kR⁷ (wherein k and R⁷ have the same significances as defined above), -
5 CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above), -
CH=C(CO₂R^{33B})₂ (wherein R^{33B} has the same significance as defined above) or -
C≡C(CH₂)_nR¹³ (wherein n and R¹³ have the same significances as defined above).]

Process 6

10 Compound (I-6), i.e., Compound (I) wherein either of R¹ and R² is NR¹⁴R¹⁵ (wherein R¹⁴ and R¹⁵ have the same significances as defined above), and the other is -CO(CH₂)_jR⁴ (wherein j and R⁴ have the same significances as defined above), -(CH₂)_kR⁷ (wherein k and R⁷ have the same significances as defined above), -CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above), -CH=C(CO₂R^{33A})₂ (wherein R^{33A} has the same
15 significance as defined above) or -C≡C(CH₂)_nR¹³ (wherein n and R¹³ have the same significances as defined above), can be prepared from Compound (I-5) wherein either of R^{1e} and R^{2e} is nitro according to the process described in Japanese Published Unexamined Patent Application No. 295588/88.

Process 7

20 Compound (Ib), i.e., Compound (I) wherein R³ is hydrogen, can also be prepared from Compound (Ia), i.e., Compound (I) wherein R³ is acyl as defined above, according to the process described in Japanese Published Unexamined Patent Application No. 295588/88.

Process 8

25 Compound (I-7), i.e., Compound (I) wherein at least one of R¹ and R² is -CH(OH)(CH₂)_bR^{4A} (wherein b and R^{4A} have the same significances as defined above) can be obtained by reduction of a compound which can be synthesized according to the above Step 1-1 or 1-2, for example, reaction with a reducing agent such as sodium borohydride in a solvent such as
30 methanol and methanol/chloroform. The reducing agent is used in an amount of 1 to 20 equivalents based on the raw material. The reaction is usually carried out at -10 to 50°C for 0.5 to 24 hours.

Process 9

Compound (I-8), i.e., Compound (I) wherein either of R¹ and R² is formyl, and the other is -(CH₂)_kR⁷ (wherein k and R⁷ have the same significances as defined above), -CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above), or -C≡C(CH₂)_nR¹³ (wherein n and R¹³ have the same significances as defined above), can be prepared according to Processes 2 to 4 after formylation of K-252a derivative (which can be prepared according to the process described in Reference Examples) wherein either of R¹ and R² is hydrogen and the other is bromine or iodine or both R¹ and R² are bromine or iodine.

Process 10

Compound (I-9), i.e., Compound (I) wherein either of R¹ and R² is -CH(SR³⁴)₂ (wherein R³⁴ has the same significance as defined above), and the other is -(CH₂)_kR⁷ (wherein k and R⁷ have the same significances as defined above), -CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above), or -C≡C(CH₂)_nR¹³ (wherein n and R¹³ have the same significances as defined above), can be obtained by subjecting Compound (I-8) to reaction with Compound (X) represented by formula (X):

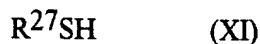


(wherein R³⁴ has the same significance as defined above) in the presence of an acid catalyst such as BF₃·OEt₂.

Each of Compound (X) and the acid catalyst is used in an amount of 1 to 20 equivalents based on Compound (I-8). The reaction is usually carried out at 0 to 80°C for 1 to 24 hours.

Process 11

Compound (I-10), i.e., Compound (I) wherein either of R¹ and R² is -CH₂R^{35A} (wherein R^{35A} has the same significance as R³⁵ except tri-lower alkylsilyloxy), and the other is -(CH₂)_kR⁷ (wherein k and R⁷ have the same significances as defined above), -CH=CH(CH₂)_mR¹² (wherein m and R¹² have the same significances as defined above), or -C≡C(CH₂)_nR¹³ (wherein n and R¹³ have the same significances as defined above), can be obtained by reduction of Compound (I-9) with a reducing agent such as sodium borohydride to form a compound wherein either of R¹ and R² is -CH₂OH, and then reaction with Compound (XI) represented by formula (XI):



(wherein R^{27} has the same significance as defined above) or Compound (XII) represented by formula (XII):



(wherein R^{29} has the same significance as defined above) in the presence of an acid catalyst such as camphorsulfonic acid.

10 The acid catalyst is used in an amount of 0.1 to 5 equivalents base on Compound (I-9), and Compound (XI) or (XII) is used in an amount of 1 to 20 equivalents based on Compound (I-9). The reaction is usually carried out at 0 to 80°C for 1 to 100 hours.

Conversion of the functional groups in the substituents in R^1 and R^2 may be carried out according to the above steps or by known methods [see, e.g. R.C. Larock, *Comprehensive Organic Transformations* (1989)].

15 For example, conversion of the functional groups can be carried out by reacting Compound (I) containing a leaving group (e.g., chlorine, bromine, iodine or sulfonyloxy such as methylsulfonyloxy, trifluoromethanesulfonyloxy and p-toluenesulfonyloxy) in R^1 or R^2 with a nucleophilic reagent such as amine, alcohol, thiol and azide in the presence of a base such as potassium carbonate to give new Compound (I).

20 Alternatively, when Compound (I) contains an azide groups in R^1 or R^2 , the functional groups can be converted into amino groups by using a reducing agent such as triphenylphosphine, or the amino groups can be reacted with lower alkyl isocyanate or di-lower alkyl carbonate to obtain an urea derivative or carbamate.

25 The desired compounds in the processes described above can be isolated and purified by appropriate combinations of purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, crystallization, and various kinds of chromatography. The intermediates may be subjected to the subsequent reaction without purification.

30 There may be stereoisomers such as geometrical isomers and optical isomers for Compound (I), and the present invention covers all possible isomers and their mixtures in any proportions.

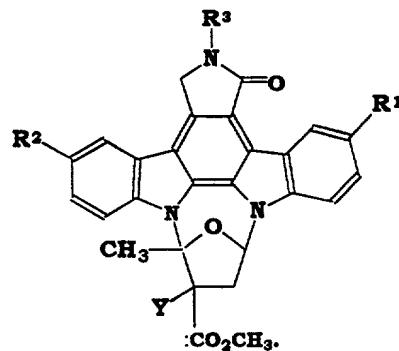
 In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free state and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid to form a salt. Compound (I) and pharmaceutically acceptable salts

thereof may be in the form of adducts with water or various solvents, which are also within the scope of the present invention.

Examples of Compound (I) are shown in Table 1 and the intermediates are shown in Table 2.

5

Table 1(1)



10

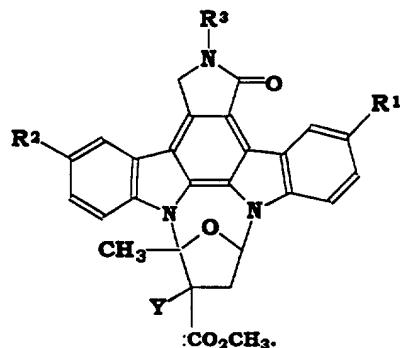
Compound	R ¹	R ²	R ³	Y
1	CH=CHCO ₂ Me	CH=CHCO ₂ Me	H	OH
2	CH=CHCO ₂ Et	H	H	OH
3	CH=CHCO ₂ Et	CH=CHCO ₂ Et	H	OH
4	CH=CHCO ₂ Me	H	H	OH
5	CH=CH-C ₆ H ₅	H	H	OH
6	CH=CH-C ₆ H ₅	CH=CH-C ₆ H ₅	H	OH
7	CH=CH-2-Pyr	H	H	OH
8	CH=CH-2-Pyr	CH=CH-2-Pyr	H	OH
9	CH ₂ CH ₂ -C ₆ H ₅	CH ₂ CH ₂ -C ₆ H ₅	H	OH
10	CH ₂ CH ₂ -C ₆ H ₅	H	H	OH
11	CH ₂ CH ₂ -2-Pyr	CH ₂ CH ₂ -2-Pyr	H	OH

Table 1(2)

Compound	R ¹	R ²	R ³	Y
12	H	CH=CHCO ₂ Et	H	OH
13	H	CH=CH-2-Pyr	H	OH
14	H	CH ₂ CH ₂ -2-Pyr	H	OH
15	NO ₂	CH=CH-2-Pyr	Ac	OAc
16	NO ₂	CH=CH-2-Pyr	H	OH
17	NH ₂	CH ₂ CH ₂ -2-Pyr	Ac	OAc
18	NH ₂	CH ₂ CH ₂ -2-Pyr	H	OH
19	NHCONHEt	CH ₂ CH ₂ -2-Pyr	H	OH

5 Pyr = Pyridyl

Table 1(3)



5

Compound	R ¹	R ²	R ³	Y
20	C≡CCH ₂ NMe ₂	C≡CCH ₂ NMe ₂	H	OH
21	C≡CCH ₂ OMe	I	H	OH
22	C≡CCH ₂ OMe	C≡CCH ₂ OMe	H	OH
23	C≡CCH ₂ OH	C≡CCH ₂ OH	H	OH
24	COCH ₂ Cl	COCH ₂ Cl	Ac	OAc
25	COCH ₂ -1-Pip	COCH ₂ -1-Pip	H	OH
26	COCH ₂ CH ₂ Cl	H	Ac	OAc
27	COCH ₂ CH ₂ Cl	COCH ₂ CH ₂ Cl	Ac	OAc
28	COCH ₂ CH ₂ -1-Pip	H	H	OH
29	COCH ₂ CH ₂ -1-Pip	COCH ₂ CH ₂ -1-Pip	H	OH
30	COCH ₂ CH ₂ -1-Morph	COCH ₂ CH ₂ -1-Morph	H	OH
31	COCH ₂ -1-Morph	COCH ₂ -1-Morph	H	OH
32	COCH ₂ NMe ₂	COCH ₂ NMe ₂	H	OH

Pip = Piperidine

Morph = Morpholine

Table 1(4)

Compound	R ¹	R ²	R3	Y
33a	COCH ₂ Cl	H	Ac	OAc
33b	H	COCH ₂ Cl	Ac	OAc
34	COCH ₂ NMe ₂	H	H	OH
35	COCH ₂ -1-THP	H	H	OH
36a	COCH ₂ -1-Morph	H	Ac	OAc
36b	H	COCH ₂ -1-Morph	Ac	OAc
37a	COCH ₂ -1-Morph	H	H	OH
37b	H	COCH ₂ -1-Morph	H	OH
38	COCH ₂ -1-THP	COCH ₂ -1-THP	H	OH
39	COCH ₂ -1-Pipz(4-Me)	COCH ₂ -1-Pipz(4-Me)	Ac	OAc
40	COCH ₂ -1-Pipz(4-Me)	COCH ₂ -1-Pipz(4-Me)	H	OH
41	H	COCH ₂ SEt	H	OH
42a	COCH ₂ S-4-Pyr	H	H	OH
42b	H	COCH ₂ S-4-Pyr	H	OH
43	COCH ₂ SMe	COCH ₂ SMe	H	OH
44	COCH ₂ SEt	COCH ₂ SEt	H	OH
45	COCH ₂ SCH ₂ Et	COCH ₂ SCH ₂ Et	H	OH
46	COCH ₂ S(CH ₂) ₂ OH	COCH ₂ S(CH ₂) ₂ OH	H	OH
47	COCH ₂ S-4-Pyr	COCH ₂ S-4-Pyr	H	OH
48	COCH ₂ S-2-Pyr	COCH ₂ S-2-Pyr	H	OH
49	COCH ₂ S-2-Pyrm	COCH ₂ S-2-Pyrm	H	OH
50	COCH ₂ S-C ₆ H ₄ (4-OH)	COCH ₂ S-C ₆ H ₄ (4-OH)	H	OH

THP = Tetrahydropyrrrole

5 Pipz = Piperazine

Pyrm = Pyrimidine

Table 1(5)

Compound	R ¹	R ²	R ³	Y
51	COCH ₂ S-2-Thiazi	COCH ₂ S-2-Thiazi	H	OH
52	COCH ₂ S-5-Tet(1-Me)	COCH ₂ S-5-Tet(1-Me)	H	OH
53	CO(CH ₂) ₂ SMe	CO(CH ₂) ₂ SMe	H	OH
54	CO(CH ₂) ₂ OMe	CO(CH ₂) ₂ OMe	H	OH
55	Br	CO(CH ₂) ₃ H	H	OH
56	CO(CH ₂) ₄ H	CO(CH ₂) ₄ H	Ac	OAc
57	COCH ₂ Br	COCH ₂ Br	Ac	OAc
58	CH(OH)Me	H	Ac	OAc
59	CH(OH)(CH ₂) ₂ Cl	CH(OH)(CH ₂) ₂ Cl	H	OH
60	CH(OH)CH ₂ -1-Pipz(4-Me)	CH(OH)CH ₂ -1-Pipz(4-Me)	H	OH
61	C≡CCH ₂ NMe ₂	H	H	OH
62	Br	C≡CCH ₂ NMeBn	H	OH
63	CH=CHCH ₂ NMe ₂	CH=CHCH ₂ NMe ₂	Ac	OAc
64	CH=CHCH ₂ NMe ₂	CH=CHCH ₂ NMe ₂	H	OH
65	CH=CHEt	H	Ac	OAc
66	CH=CHEt	H	H	OH
67	CH=CHEt	I	Ac	OAc
68	CH=CHEt	CH=CHEt	H	OH
69	(CH ₂) ₂ Cl	(CH ₂) ₂ Cl	H	OH
70a	(CH ₂) ₂ I	(CH ₂) ₂ I	H	OH
70b	(CH ₂) ₂ OCOOH	(CH ₂) ₂ OCOOH	H	OH

Thiazi = Thiazoline

5 Tet = Tetrazole

Table 1(6)

Compound	R ¹	R ²	R ³	Y
70c	(CH ₂) ₂ OH	(CH ₂) ₂ OH	H	
71	(CH ₂) ₂ OCO-4-Pyr	(CH ₂) ₂ OCO-4-Pyr	?	H
72a	CH ₂ CO ₂ Me	H	H	
72b	CH ₂ CO ₂ Me	CH ₂ CO ₂ Me	H	
73a	(CH ₂) ₃ I	(CH ₂) ₃ I	H	OH
73b	(CH ₂) ₃ OCOH	(CH ₂) ₃ OCOH	H	OH
73c	(CH ₂) ₃ OH	(CH ₂) ₃ OH	H	OH
74	(CH ₂) ₃ OMe	(CH ₂) ₃ OMe	H	OH
75	(CH ₂) ₂ -1-Pip	(CH ₂) ₂ -1-Pip	H	OH
76	(CH ₂) ₂ -1-Morph	(CH ₂) ₂ -1-Morph	H	OH
77	(CH ₂) ₂ NEt ₂	(CH ₂) ₂ NEt ₂	H	OH
78	(CH ₂) ₂ NMe(CH ₂) ₂ OH	(CH ₂) ₂ NMe(CH ₂) ₂ OH	H	OH
79	(CH ₂) ₂ NHMe	(CH ₂) ₂ NHMe	H	OH
80	(CH ₂) ₂ NHCH ₂ C ₆ H ₄ (4-MeO)	(CH ₂) ₂ NHCH ₂ C ₆ H ₄ (4-MeO)	H	OH
81	(CH ₂) ₂ N ₃	(CH ₂) ₂ N ₃	H	OH
82	(CH ₂) ₃ -1-Pip	(CH ₂) ₃ -1-Pip	H	OH
83	(CH ₂) ₃ -1-Morph	(CH ₂) ₃ -1-Morph	H	OH
84	(CH ₂) ₃ NEt ₂	(CH ₂) ₃ NEt ₂	H	OH
85	(CH ₂) ₃ NHCONHEt	(CH ₂) ₃ NHCONHEt	H	OH
86	(CH ₂) ₃ NHCO ₂ f-Bu	(CH ₂) ₃ NHCO ₂ f-Bu	H	OH
87	(CH ₂) ₂ SMe	(CH ₂) ₂ SMe	H	OH
88	(CH ₂) ₂ SEt	(CH ₂) ₂ SEt	H	OH
89	(CH ₂) ₂ SCH ₂ CO ₂ Me	(CH ₂) ₂ SCH ₂ CO ₂ Me	H	OH

Table 1(7)

Compound	R ¹	R ²	R ³	Y
90	(CH ₂) ₂ S(CH ₂) ₂ CO ₂ Et	(CH ₂) ₂ S(CH ₂) ₂ CO ₂ Et	H	OH
91	(CH ₂) ₂ S-C ₆ H ₄ (4-OH)	(CH ₂) ₂ S-C ₆ H ₄ (4-OH)	H	OH
92	(CH ₂) ₂ S-2-Thiazl	(CH ₂) ₂ S-2-Thiazl	H	OH
93	(CH ₂) ₂ S-4-Pyr	(CH ₂) ₂ S-4-Pyr	H	OH
94	(CH ₂) ₂ S-2-Pyr	(CH ₂) ₂ S-2-Pyr	H	OH
95	(CH ₂) ₃ SMe	(CH ₂) ₃ SMe	H	OH
96	(CH ₂) ₃ S-2- (Benz)Thiazole	(CH ₂) ₃ S-2- (Benz)Thiazole	H	OH
97	CH=CH-2-Pyr	CHO	Ac	OAc
98	CH=CH-2-Pyr	CH ₂ OH	Ac	OAc
99	CH=CH-2-Pyr	CH ₂ OH	H	OH
100	CH=CH-2-Pyr	CH ₂ OSiMe ₂ t-Bu	Ac	OAc
101	CH=CH-2-Pyr	CH ₂ OSiMe ₂ t-Bu	H	OH
102	CH=CH-2-Pyr	CH ₂ OMe	H	OH
103	CH=CH-2-Pyr	CH ₂ OEt	H	OH
104	CH=CH-2-Pyr	CH ₂ O(CH ₂) ₂ NMe ₂	H	OH
105	CH=CH-2-Pyr	CH ₂ SEt	H	OH
106	CH=CH-2-Pyr	CH ₂ S(CH ₂) ₂ NMe ₂	H	OH
107	CH=CH-2-Pyr	CH ₂ S-2-(Benz)Imid	H	OH
108	CH=CH-2-Pyr	CH ₂ S-2-Pyr	H	OH
109	CH=CH-2-Pyr	CH(SEt) ₂	Ac	OAc
110	CH=CH-2-Pyr	CH(SEt) ₂	H	OH
111	CHO	CH=CH-2-Pyr	Ac	OAc
112	CH ₂ OH	CH=CH-2-Pyr	Ac	OAc

5 Imid = Imidazole

(Benz)Thiazole = Benzothiazole

Table 1(8)

Compound	R ¹	R ²	R ³	Y
113	CH ₂ OH	CH=CH-2-Pyr	H	OH
114	CH ₂ OSiMe ₂ <i>t</i> -Bu	CH=CH-2-Pyr	Ac	OAc
115	CH ₂ OSiMe ₂ <i>t</i> -Bu	CH=CH-2-Pyr	H	OH
116	CH ₂ OMe	CH=CH-2-Pyr	H	OH
117	CH ₂ OEt	CH=CH-2-Pyr	H	OH
118	CH ₂ SEt	CH=CH-2-Pyr	H	OH
119	CH ₂ S-2-Pyr	CH=CH-2-Pyr	H	OH
120	CH ₂ S-2-(Benz)Imid	CH=CH-2-Pyr	H	OH
121	CH=CHEt	CH=CH-2-Pyr	Ac	OAc
122	CH=CHEt	CH=CH-2-Pyr	H	OH
123	(CH ₂) ₂ -2-Pyr	CH ₂ OSiMe ₂ <i>t</i> -Bu	Ac	OAc
124	(CH ₂) ₂ -2-Pyr	CH ₂ OSiMe ₂ <i>t</i> -Bu	H	OH
125a	(CH ₂) ₂ -2-Pyr	CH ₂ OMe	Ac	OAc
125b	(CH ₂) ₂ -2-Pyr	CH ₂ OMe	H	OAc
126	(CH ₂) ₂ -2-Pyr	CH ₂ OMe	H	OH
127a	(CH ₂) ₂ -2-Pyr	CH ₂ OEt	H	OH
127b	(CH ₂) ₂ -2-Pyr	CH ₂ OH	H	OH
128	(CH ₂) ₂ -2-Pyr	CH ₂ S-2-Pyr	Ac	OAc
129	(CH ₂) ₂ -2-Pyr	CH ₂ S-2-Pyr	H	OH
130	CH ₂ OSiMe ₂ <i>t</i> -Bu	(CH ₂) ₂ -2-Pyr	Ac	OAc
131	CH ₂ OSiMe ₂ <i>t</i> -Bu	(CH ₂) ₂ -2-Pyr	H	OH
132	CH ₂ OMe	(CH ₂) ₂ -2-Pyr	H	OH
133	CH ₂ OEt	(CH ₂) ₂ -2-Pyr	H	OH

5 (Benz)Imid = Benzimidazole

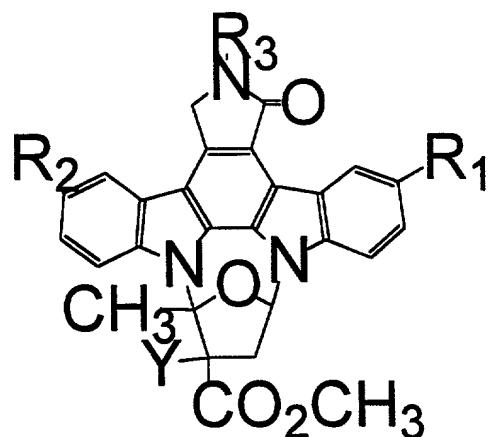
Table 1(9)

Compound	R ¹	R ²	R ³	Y
134	CH ₂ SEt	(CH ₂) ₂ -2-Pyr	H	OH
135	CH ₂ S(CH ₂) ₂ NMe ₂	(CH ₂) ₂ -2-Pyr	H	OH
136	CH ₂ S-2-Pyr	(CH ₂) ₂ -2-Pyr	Ac	OAc
137	CH ₂ S-2-Pyr	(CH ₂) ₂ -2-Pyr	H	OH
*138	C≡CCH ₂ OMe	C≡CCH ₂ OMe	H	OH
139	CH ₂ CH ₂ CO ₂ Me	CH ₂ CH ₂ CO ₂ Me	H	OH
140	CH ₂ CH ₂ CO ₂ Et	CH ₂ CH ₂ CO ₂ Et	H	OH
141	Br	CH=CH-2-Pyr	Ac	OAc
142	Br	CH=CH-2-Pyr	H	OH
143	Br	CH ₂ CH ₂ -2-Pyr	H	OH
144	CH=CH-4-Pyr	CH=CH-4-Pyr	Ac	OAc
145	CH=CH-4-Pyr	CH=CH-4-Pyr	H	OH
146	CH ₂ CH ₂ -4-Pyr	CH ₂ CH ₂ -4-Pyr	H	OH
147	CH=CH-2-Imid	H	Ac	OAc
148	CH=CH-2-Imid	H	H	OH
149	CH ₂ CH ₂ -2-Imid	H	H	OH
150	CH=C(CO ₂ Me) ₂	CH=C(CO ₂ Me) ₂	Ac	OAc
151	CH ₂ CH(CO ₂ Me) ₂	CH ₂ CH(CO ₂ Me) ₂	Ac	OAc
152	CH ₂ CH(CO ₂ Me) ₂	CH ₂ CH(CO ₂ Me) ₂	H	OH
153	n-C ₄ H ₉	(CH ₂) ₂ -2-Pyr	H	OH
154	CH ₂ OCH ₂ OMe	H	H	OH
155	CH ₂ OCH ₂ OMe	CH ₂ OCH ₂ OMe	H	OH
156	CH ₂ OCH ₂ OEt	CH ₂ OCH ₂ OEt	H	OH
157	CH ₂ O(CH ₂) ₂ OMe	CH ₂ O(CH ₂) ₂ OMe	H	OH

5 * The CO₂CH₃ group is replaced with CH₂OH.

Tab.2

Table 2



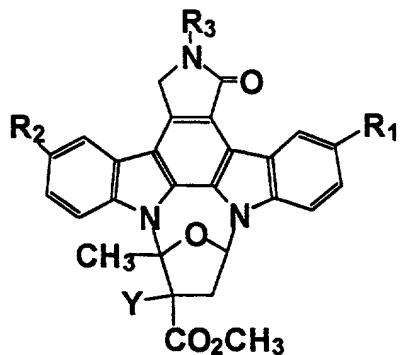
Compound	R1	R2	R3	Y
A	Br	H	Ac	OAc
B	Br	CHO	Ac	OAc
C	H	CHO	Ac	OAc
D	NO ₂	H	Ac	OAc
E	NO ₂	CHO	Ac	OAc
F	—	—	Ac	OAc
G	—	—	H	OH
H	—	H	Ac	OAc
I	Br	—	Ac	OAc
J	CHO	—	Ac	OAc
K	CH ₂ OH	—	Ac	OAc

EXAMPLES

Certain embodiments of the invention are illustrated in the following Examples and
5 Reference Examples.

Compounds a-e and g which are known compounds used as the starting compounds are described in Japanese Published Unexamined Patent Application No. 295588/88. Compounds f and h are described in WO94/02488. The structures are shown below in Figure 9.

Fig. 9



Compound	R ¹	R ²	R ³	Y
a	CHO	CHO	Ac	OAc
b	CHO	H	Ac	OAc
c	H	H	Ac	OAc
d	Ac	H	Ac	OAc
e	CH ₂ OH	H	Ac	OAc
f	CH ₂ OH	CH ₂ OH	Ac	OAc
g	Ac	Ac	Ac	OAc
h	CH ₂ OH	CH ₂ OH	H	OH

5

Example 1 **Synthesis of Compound 1**

Step A:

10 To a solution of 50.0 mg (0.0824 mmol) of Compound a (Japanese Published Unexamined Patent Application No. 295588/88) in 5 ml of chloroform was added 198 mg (0.592 mmol) of methyl(triphenylphosphoranylidene)acetate, followed by stirring under reflux for 4 hours. After cooling, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 98/2) to give diacetylated Compound 1.

FAB-MS (m/z) ; 720 (M+1)⁺

Step B:

5 To a solution of 71.0 mg of diacetylated Compound 1 in a mixture of 4 ml of 1,2-dichloromethane and 1 ml of methanol was added 18 ml (0.09 mmol) of 5.1 N sodium methoxide/methanol solution, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was poured into water, followed by extraction with tetrahydrofuran. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the residue was crystallized from 10 chloroform-methanol to give 16.3 mg (yield from Compound a: 31%) of Compound 1.

15 ¹H-NMR (DMSO-d₆) δ; 2.04 (dd, 1H, J = 4.9, 14.1 Hz), 2.12 (s, 3H), 3.42 (dd, 1H, J = 7.5, 14.1 Hz), 3.77 (s, 6 H), 3.93 (s, 3H), 5.10 (s, 2H), 6.43 (s, 1H), 6.59 (d, 1H, J = 15.9 Hz), 6.78 (d, 1H, J = 15.9 Hz), 7.21 (dd, 1H, J = 4.9, 7.5 Hz), 7.85 (d, 1H, J = 15.9 Hz), 7.95 (d, 1H, J = 15.9 Hz), 7.88 - 8.00 (m, 4 H), 8.40 (d, 1H, J = 1.2 Hz), 8.79 (s, 1H), 9.48 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z) ; 636 (M+1)⁺

20 **Example 2 Synthesis of Compound 2**

The same procedure as in Example 1, Step A was repeated using 55.7 mg (0.0962 mmol) of Compound b (Japanese Published Unexamined Patent Application No. 295588/88) and 92.1 mg (0.264 mmol) of ethyl(triphenylphosphoranylidene)acetate to give diacetylated Compound 2.

25 FAB-MS (m/z) ; 650 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound 2 to give 27.5 mg (yield from Compound b: 51%) of Compound 2.

¹H-NMR (DMSO-d₆) δ; 1.31 (t, 3H, J = 7.1 Hz), 2.05 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 3.41 (dd, 1H, J = 7.3, 14.1 Hz), 3.93 (s, 3H), 4.23 (q, 2H, J = 7.1 Hz), 5.00 (d, 1H, J = 17.5 Hz), 5.06 (d, 1H, J = 17.5 Hz), 6.36 (s, 1H), 6.56 (d, 1H, J = 15.9 Hz), 7.19 (dd, 1H, J = 4.9, 7.3 Hz), 7.84 (d, 1H, J = 15.9 Hz), 7.36 - 8.08 (m, 6 H), 8.69 (s, 1H), 9.47 (d, 1H, J = 1.5 Hz).

5 FAB-MS (m/z) ; 565 (M)⁺, 566 (M+1)⁺

Example 3 **Synthesis of Compound 3**

10 The same procedure as in Example 1, Step A was repeated using 50.0 mg (0.0824 mmol) of Compound a and 225 mg (0.645 mmol) of ethyl (triphenylphosphoranylidene)acetate to give diacetylated Compound 3.

FAB-MS (m/z) ; 747 (M)⁺, 748 (M+1)⁺

15 The same procedure as in Example 1, Step B was repeated using diacetylated Compound 3 to give 29.7 mg (yield from Compound a: 54%) of Compound 3.

¹H-NMR (DMSO-d₆) δ; 1.31 (t, 6 H, J = 7.1 Hz), 2.04 (dd, 1H, J = 4.9, 14.2 Hz), 2.15 (s, 3H), 3.42 (dd, 1H, J = 7.4, 14.2 Hz), 3.93 (s, 3H), 4.23 (q, 2H, J = 7.1 Hz), 4.23 (q, 2H, J = 7.1 Hz), 5.10 (s, 2H), 6.43 (s, 1H), 6.58 (d, 1H, J = 15.9 Hz), 6.77 (d, 1H, J = 16.0 Hz), 7.21 (dd, 1H, J = 4.9, 7.4 Hz), 7.83 (d, 1H, J = 15.9 Hz), 7.93 (d, 1H, J = 16.0 Hz), 7.88 - 8.00 (m, 4 H), 8.40 (d, 1H, J = 1.5 Hz), 8.78 (s, 1H), 9.47 (d, 1H, J = 1.6 Hz).

20 FAB-MS (m/z) ; 664 (M+1)⁺

25

Example 4 **Synthesis of Compound 4**

The same procedure as in Example 1, Step A was repeated using 50.0 mg (0.0824 mmol) of Compound b and 104 mg (0.311 mmol) of methyl (triphenylphosphoranylidene)-acetate to give diacetylated Compound 4.

FAB-MS (m/z) ; 636 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound 4
5 to give 14.6 mg (yield from Compound b: 31%) of Compound 4.

10 ¹H-NMR (DMSO-d₆) δ; 2.05 (dd, 1H, J = 4.9, 14.2 Hz), 2.15 (s, 3H), 3.41 (dd, 1H, J = 7.5, 14.2 Hz), 3.77 (s, 3 H), 3.93 (s, 3H), 5.00 (d, 1H, J = 17.6 Hz), 5.06 (d, 1H, J = 17.6 Hz), 6.36 (s, 1H), 6.59 (d, 1H, J = 15.8 Hz), 7.19 (dd, 1H, J = 4.9, 7.5 Hz),
10 7.85 (d, 1H, J = 15.8 Hz), 7.36 - 8.08 (m, 6 H), 8.70 (s, 1H), 9.47 (d, 1H, J = 1.5 Hz).

FAB-MS (m/z) ; 552 (M+1)⁺

Example 5 Synthesis of Compound 5

15 To a solution of 215 mg (0.553 mmol) of benzyltriphenylphosphonium chloride in 2 ml of dichloromethane were added 165 mg (1.19 mmol) of potassium carbonate and 12 mg (0.045 mmol) of 18-crown-6, followed by stirring at room temperature for 5 minutes. After addition of a solution of 80.0 mg (0.138 mmol) of Compound b in 8 ml of dichloromethane, the mixture was stirred overnight at room temperature. Insoluble materials in the reaction mixture were filtered off, and the
20 solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) and then by preparative TLC (chloroform/methanol = 99/1) to give 80.0 mg (89%) of diacetylated Compound 5.

FAB-MS (m/z) ; 564 (M+1)⁺

25 The same procedure as in Example 1, Step B was repeated using 80.0 mg (0.123 mmol) of diacetylated Compound 5 to give 26.1 mg (37%) of Compound 5 (E/Z = 3/7).

10 ¹H-NMR (DMSO-d₆) δ; 2.00 - 2.57 (m, 1H), 2.13 (s, 2.1H), 2.14 (s, 0.9H), 3.37 (dd, 0.7H, J = 7.5, 14.2 Hz), 3.40 (dd, 0.3H, J = 7.6, 13.7 Hz), 3.90 (s, 2.1H), 3.92 (s, 0.9H), 4.93 - 5.60 (m, 2H), 6.33 (s, 0.7H), 6.34 (s, 0.3H), 6.621 (d, 0.7H, J = 12.4

Hz), 6.849 (d, 0.7H, J = 12.4 Hz), 7.072 (dd, 0.7H, J = 4.9, 7.5 Hz), 7.132 - 8.064 (m, 11.9H), 8.58 (s, 0.7H), 8.63 (s, 0.3H), 9.15 (m, 0.7H), 9.38 (d, 0.3H, J = 1.7 Hz).

FAB-MS (m/z) ; 570 (M+1)⁺

5

Example 6 **Synthesis of Compound 6**

The same procedure as in Example 5 was repeated using 250 mg (0.643 mmol) of benzyltriphenylphosphonium chloride and 50.0 mg (0.0824 mmol) of Compound a to give 63.5 mg of diacetylated Compound 6.

10

FAB-MS (m/z) ; 756 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 63.5 mg (0.0841 mmol) of diacetylated Compound 6 to give 49.9 mg (yield from Compound a: 90%) of Compound 6 (R¹, R²: 15 cis, trans / R¹, R²: cis, cis / R¹, R²: trans, cis / R¹, R²: trans, trans = 2/1/1/1).

20

¹H-NMR (DMSO-d₆) δ; 1.99 - 2.08 (m, 1H), 2.10, 2.12, 2.15, 2.17 (4xs, 3H), 3.35 - 3.45 (m, 1H), 3.89, 3.92, 3.92, 3.93 (4xs, 3H), 4.50 - 5.03 (m, 2H), 6.35, 6.36, 6.40, 6.41 (4xs, 1H), 6.61 - 8.23 (m, 20H), 8.59, 8.57, 8.67, 8.72 (m, 1H), 9.13, 9.17, 9.36, 9.40 (m, 1H).

FAB-MS (m/z) ; 672 (M+1)⁺

Example 7 **Synthesis of Compound 7**

The same procedure as in Example 5 was repeated using 61.8 mg (0.142 mmol) of 2-25 pyridinemethyl-triphenylphosphonium bromide and 26.5 mg (0.0458 mmol) of Compound b to give 47.3 mg of diacetylated Compound 7.

FAB-MS (m/z) ; 655 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 47.3 mg of diacetylated Compound 7 to give 13.3 mg (yield from Compound b: 51%) of Compound 7.

¹H-NMR (DMSO-d₆) δ; 2.05 (dd, 1H, J = 5.0, 14.1 Hz), 2.16 (s, 3H), 3.42 (dd, 1H, J = 7.3, 14.1 Hz), 3.94 (s, 3H), 5.00 (d, 1H, J = 18.0 Hz), 5.06 (d, 1H, J = 18.0 Hz), 6.35 (s, 1 H), 7.17 (dd, 1H, J = 5.0, 7.3 Hz), 7.23 - 7.97 (m, 8 H), 7.30 (d, 1H, J = 16.0 Hz), 7.89 (d, 1H, J = 16.0 Hz), 8.07 (d, 1H, J = 7.3 Hz), 8.59 (m, 1H), 8.67 (s, 1H), 9.46 (d, 1H, J = 1.2 Hz).

10

Example 8 **Synthesis of Compound 8**

The same procedure as in Example 5 was repeated using 244 mg (0.561 mmol) of 2-pyridinemethyl-triphenylphosphonium bromide and 50.0 mg (0.0824 mmol) of Compound a to give 75.3 mg of diacetylated Compound 8.

15 FAB-MS (m/z) ; 757 (M)⁺

The same procedure as in Example 1, Step B was repeated using 75.3 mg of diacetylated Compound 8 to give 22.6 mg (yield from Compound a: 41%) of Compound 8.

¹H-NMR (DMSO-d₆) δ; 2.06 (dd, 1H, J = 5.0, 14.4 Hz), 2.18 (s, 3H), 3.43 (dd, 1H, J = 7.6, 14.4 Hz), 3.95 (s, 3H), 5.08 - 5.17 (m, 2H), 6.42 (s, 1 H), 7.19 (dd, 1H, J = 5.0, 7.6 Hz), 7.30 (d, 1H, J = 16.0 Hz), 7.42 (d, 1H, J = 16.0 Hz), 7.22 - 9.46 (m, 17 H).

25 FAB-MS (m/z) ; 674 (M+1)⁺

Example 9 Synthesis of Compound 9

To a solution of 36.9 mg (0.0550 mmol) of Compound 6 in 4 ml of N,N-dimethylformamide was added 25 mg of 10% Pd/C, followed by stirring at 60°C for 2 hours in an atmosphere of hydrogen. After insoluble materials in the reaction mixture were filtered off, the

solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give 31.1 mg (84%) of Compound 9.

10 $^1\text{H-NMR}$ (DMSO-d₆) δ ; 1.98 (dd, 1H, J = 5.1, 14.1 Hz), 2.12 (s, 3H), 2.99 - 3.14 (m, 8H),
5 3.36 (dd, 1H, J = 7.5, 14.1 Hz), 3.92 (s, 3H), 4.92 (d, 1H, J = 17.6 Hz), 4.97 (d,
1H, J = 17.6 Hz), 6.28 (s, 1H), 7.08 (dd, 1H, J = 5.1, 7.5 Hz), 7.17 - 7.38 (m, 12
H), 7.78 - 7.84 (m, 3H), 8.59 (s, 1H), 9.09 (m, 1H).

FAB-MS (m/z) ; 676 (M+1)⁺

10 **Example 10 Synthesis of Compound 10**

The same procedure as in Example 9 was repeated using 43.6 mg (0.0766 mmol) of Compound 5 to give 24.2 mg (55%) of Compound 10.

10 $^1\text{H-NMR}$ (DMSO-d₆) δ ; 2.00 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 2.99 - 3.11 (m,
15 4H), 3.37 (dd, 1H, J = 7.3, 14.1 Hz), 3.92 (s, 3H), 4.97 (d, 1H, J = 17.9 Hz), 5.03
(d, 1H, J = 17.9 Hz), 6.32 (s, 1H), 7.10 (dd, 1H, J = 4.9, 7.3 Hz), 7.17 - 8.06 (m,
11 H), 8.58 (s, 1H), 9.11 (m, 1H).

FAB-MS (m/z) ; 572 (M+1)⁺

20 **Example 11 Synthesis of Compound 11**

The same procedure as in Example 9 was repeated using 15.0 mg (0.0223 mmol) of Compound 8 to give 9.8 mg (65%) of Compound 11.

10 $^1\text{H-NMR}$ (CDCl₃) δ ; 2.19 (s, 3H), 2.42 (dd, 1H, J = 4.8, 14.4 Hz), 3.21 - 3.29 (m, 8H),
25 3.31 (dd, 1H, J = 7.5, 14.4 Hz), 4.08 (s, 3H), 4.19 (br, 1H), 4.83 (d, 1H, J = 16.2
Hz), 4.88 (d, 1H, J = 16.2 Hz), 5.98 (s, 1H), 6.84 (dd, 1H, J = 4.8, 7.5 Hz), 7.11 -
7.33 (m, 7H), 7.56 - 7.62 (m, 2H), 7.68 (s, 1H), 7.73 (d, 1H, J = 8.6 Hz), 8.58 -
8.61 (m, 2H), 9.08 (m, 1H).

FAB-MS (m/z) ; 678 (M+1)⁺

Example 12 **Synthesis of Compound 12**

The same procedure as in Example 1, Step A was repeated using 25.0 mg (0.0432 mmol) of Compound C obtained in Reference Example 3 and 52.0 mg (0.156 mmol) of ethyl (triphenylphosphoranylidene)acetate to give 17.2 mg (63%) of diacetylated Compound 12.

FAB-MS (m/z) ; 650 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound 10 12 to give 8.1 mg (54%) of Compound 12.

¹H-NMR (DMSO-d₆) δ; 1.31 (t, 3 H, J = 7.1 Hz), 2.00 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 3.41 (dd, 1H, J = 7.3, 14.1 Hz), 3.93 (s, 3H), 4.23 (q, 2H, J = 7.1 Hz), 5.08 (s, 2H), 6.41 (s, 1H), 6.76 (d, 1H, J = 15.9 Hz), 7.16 (dd, 1H, J = 4.9, 7.3 Hz), 7.93 (d, 1H, J = 15.9 Hz), 7.28 - 7.96 (m, 4H), 8.39 (s, 1H), 8.71 (s, 1H), 9.23 (d, 1H, J = 7.8 Hz).

FAB-MS (m/z) ; 566 (M+1)⁺

Example 13 **Synthesis of Compound 13**

20 The same procedure as in Example 5 was repeated using 118 mg (0.855 mmol) of 2-pyridinemethyl-triphenylphosphonium bromide and 39.6 mg (0.0684 mmol) of Compound C obtained in Reference Example 3 to give diacetylated Compound 13.

FAB-MS (m/z) ; 655 (M+1)⁺

25 The same procedure as in Example 1, Step B was repeated using diacetylated Compound 13 to give 30.0 mg (yield from Compound C: 77%) of Compound 13 (E/Z = 8/2).

¹H-NMR (DMSO-d₆) δ; 2.02 (dd, 1H, J = 4.9, 14.1 Hz), 2.13 (s, 0.6H), 2.17 (s, 2.4H), 3.41 (dd, 1H, J = 7.3, 14.1 Hz), 3.92 (s, 0.6 H), 3.94 (s, 2.4H), 5.03 (d, 0.8H, J =

18.8 Hz), 5.13 (d, 0.8H, J = 18.8 Hz), 6.35 (s, 0.2H), 6.39 (s, 0.8 H), 6.69 (d, 0.2H, J = 12.9 Hz), 6.98 (d, 0.2H, J = 12.9 Hz), 7.15 (dd, 1H, J = 4.9, 7.3 Hz), 7.24 - 7.97 (m, 8 H), 7.42(d, 0.8H, J = 16.0 Hz), 7.96 (d, 0.8H, J = 16.0 Hz), 8.23 (s, 0.2H), 8.30 (s, 0.8H), 8.60 (m, 1H), 8.70 (s, 1H), 9.18 (d, 0.2H, J = 7.8 Hz), 9.23 (d, 0.8H, J = 7.8 Hz).

5

FAB-MS (m/z) ; 571 (M+1)⁺

Example 14 **Synthesis of Compound 14**

The same procedure as in Example 9 was repeated using 19.9 mg (0.0349 mmol) of 10 Compound 13 to give 16.4 mg (82%) of Compound 14.

¹H-NMR (CDCl₃) δ; 1.99 (dd, 1H, J = 4.9, 14.2 Hz), 2.13 (s, 3H), 3.16 - 3.24 (m, 4H), 3.38 (dd, 1H, J = 7.4, 14.2 Hz), 3.92 (s, 3H), 4.30 (d, 1H, J = 17.4 Hz), 4.98 (d, 1H, J = 17.4 Hz), 6.29 (s, 1 H), 7.12 (dd, 1H, J = 4.9, 7.4 Hz), 7.21 - 7.89 (m, 9H), 8.55 (m, 1H), 8.61 (s, 1H), 9.21 (d, 1H, J = 7.6 Hz).

15

FAB-MS (m/z) ; 573 (M+1)⁺

Example 15 **Synthesis of Compound 15**

The same procedure as in Example 5 was repeated using 144 mg (0.331 mmol) of 20 2-pyridinemethyl-triphenylphosphonium bromide and Compound E obtained in Reference Example 5 to give 36.3 mg (yield from Compound D: 62%) of Compound 15 (E/Z = 9/1).

¹H-NMR (CDCl₃) δ; 1.81 (s, 0.3H), 1.84 (s, 2.7H), 2.25 (dd, 1H, J = 5.2, 14.7 Hz), 2.29 (s, 0.3H), 2.33 (s, 2.7H), 2.65 (s, 2.7H), 2.68 (s, 0.3H), 4.01 (s, 0.3H), 4.04 (s, 2.7H), 4.07 (dd, 1H, J = 7.6, 14.7 Hz), 5.08 (m, 0.2H), 5.34 (m, 1.8H), 6.81 (d, 0.1H, J = 12.6 Hz), 6.98 (dd, 1H, J = 5.2, 7.6 Hz), 7.19 (m, 1H), 7.32 (d, 0.9H, J = 16.1 Hz), 7.87 (d, 1H, J = 16.1 Hz), 7.95 (d, 1H, J = 8.8 Hz), 8.13 (m, 1H), 8.35 (m, 1H), 8.66 (m, 1H), 9.93 (m, 1H).

FAB-MS (m/z) ; 700 (M+1)⁺

Example 16 **Synthesis of Compound 16**

The same procedure as in Example 1, Step B was repeated using 33.1 mg (0.0474 mmol) of Compound 15 to give 24.5 mg (84%) of Compound 16 (E/Z = 9/1).

5 FAB-MS (m/z) ; 616 (M+1)⁺

¹H-NMR (DMSO-d₆) δ; 2.13 (dd, 1H, J = 5.0, 14.3 Hz), 2.18 (s, 3H), 3.47 (dd, 1H, J = 7.5, 14.3 Hz), 3.93 (s, 0.3 H), 3.95 (s, 2.7H), 5.13 (d, 0.9H, J = 18.1 Hz), 5.18 (d, 0.9H, J = 18.1 Hz), 6.45 (s, 0.1 H), 6.49 (s, 0.9 H), 6.71 (d, 0.1H, J = 12.6 Hz), 6.99 (d, 0.1H, J = 12.6 Hz), 7.30 (dd, 1H, J = 5.0, 7.5 Hz), 7.24 - 8.60 (m, 9 H), 10 7.43 (d, 0.9H, J = 16.0 Hz), 7.96 (d, 0.9H, J = 16.0 Hz), 8.74 (s, 0.1H), 8.88 (s, 0.9H), 10.14 (d, 0.1H, J = 2.4 Hz), 10.17 (d, 0.9H, J = 2.4 Hz).

Example 17 **Synthesis of Compound 17**

Compound 15 (133 mg, 0.190 mmol) was subjected to catalytic reduction in the same 15 manner as in Example 9 to give 93.2 mg (73%) of Compound 17.

¹H-NMR (DMSO-d₆) δ; 1.68 (s, 3H), 2.09 (dd, 1H, J = 4.9, 14.6 Hz), 2.18 (s, 3H), 2.71 (s, 3H), 3.15 - 3.21 (m, 2H), 3.82 (dd, 1H, J = 7.4, 14.6 Hz), 3.93 (s, 3H), 4.97 (br, 2H), 5.35 (s, 2H), 7.11 (dd, 1H, J = 4.2, 7.4 Hz), 6.90 - 7.87 (m, 8H), 8.32 (d, 20 1H, J = 2.2 Hz), 8.55 (m, 1H).

FAB-MS (m/z) ; 672 (M+1)⁺

Example 18 **Synthesis of Compound 18**

The same procedure as in Example 1, Step B was repeated using 23.6 mg (0.0352 mmol) of Compound 17 to give 16.3 mg (79%) of Compound 18.

5 FAB-MS (m/z) ; 588 (M+1)⁺

Example 19 **Synthesis of Compound 19**

To a solution of 66.2 mg (0.0987 mmol) of Compound 17 in 4 ml of chloroform were added 0.02 ml of triethylamine and 0.1 ml of ethyl isocyanate, followed by stirring at room temperature for 10 2 hours. After addition of water, the reaction mixture was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 99/1 - 98/2) to give 68.7 mg (94%) of diacetylated Compound 19.

15 FAB-MS (m/z) ; 743 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 25.5 mg (0.0344 mmol) of diacetylated Compound 19 to give 17.7 mg (78%) of Compound 19.

20 ¹H-NMR (DMSO-d₆) δ; 1.08 (t, 3H, J = 7.1 Hz), 1.94 (dd, 1H, J = 4.6, 14.1 Hz), 2.11 (s, 3H), 3.10 - 3.22 (m, 4H), 3.34 (dd, 1H, J = 7.2, 14.1 Hz), 3.90 (s, 3H), 4.90 (d, 1H, J = 17.5 Hz), 4.96 (d, 1H, J = 17.5 Hz), 6.00 (t, 1H, J = 5.4 Hz), 6.26 (s, 1H), 7.03 (dd, 1H, J = 4.6, 7.2 Hz), 7.22 - 7.86 (m, 8 H), 8.43 (s, 1H), 8.55 (m, 1H), 25 8.58 (s, 1H), 8.84 (d, 1H, J = 2.2 Hz).

FAB-MS (m/z) ; 659 (M+1)⁺

Example 20 **Synthesis of Compound 20**

To a solution of 40 mg (0.05 mmol) of Compound F obtained in Reference Example 6 in 30 ml of a dichloromethane/diethylamine mixture (2/1) were added 26 mg (0.025 mmol) of

palladium(II) acetate, 13 mg (0.05 mmol) of triphenylphosphine and 9.5 mg (0.05 mmol) of cuprous iodide in a stream of argon, followed by stirring at room temperature for 10 minutes. After addition of 0.16 ml (1.5 mmol) of N,N-dimethylpropargylamine, the mixture was stirred at room temperature for one hour. The solvent was evaporated under reduced pressure, and the residue was purified by 5 silica gel column chromatography (chloroform/methanol = 96/4) to give 15.1 mg (42%) of diacetylated Compound 20.

FAB-MS (m/z) ; 714 (M+1)⁺

10 The same procedure as in Example 1, Step B was repeated using 6.5 mg (0.0091 mmol) of diacetylated Compound 20 to give 2.0 mg (35%) of Compound 20.

15 ¹H-NMR (CDCl₃) δ ; 2.14 (s, 3H), 2.46 (s, 6H), 2.48 (s, 6H), 3.05 (dd, 1H, J = 4.5, 14.4 Hz), 3.55 (s, 2H), 3.56 (s, 2H), 3.62 (dd, 1H, J = 7.5, 14.4 Hz), 4.08 (s, 3H), 4.54 (d, 1H, J = 16.9 Hz), 4.70 (d, 1H, J = 16.9 Hz), 5.33 (m, 2H), 6.76 (dd, 1H, J = 4.5, 7.5 Hz), 7.15 (d, 1H, J = 8.5 Hz), 7.34 (dd, 1H, J = 1.3, 8.5 Hz), 7.61 (dd, 1H, J = 1.3, 8.5 Hz), 7.91 (d, 1H, J = 8.8 Hz), 7.96 (d, 1H, J = 0.97 Hz), 8.85 (s, 1H).

FAB-MS (m/z) ; 630 (M+1)⁺

20 **Example 21** **Synthesis of Compound 21 and Compound 22**

A mixture of 2.2 mg (0.01 mmol) of palladium(II) acetate, 5.0 mg (0.02 mmol) of triphenylphosphine and 1 ml of dichloromethane was stirred at room temperature for 5 minutes in a stream of argon. To the mixture was added a solution of 72 mg (0.1 mmol) of Compound G obtained in Reference Example 7 and 3.8 mg (0.02 mmol) of cuprous iodide in 3 ml of a 25 dichloromethane/diethylamine mixture (2/1), followed by stirring at room temperature for 10 minutes. After addition of 0.056 ml (1 mmol) of 1-methoxy-2-propyne, the mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform) to give 23.0 mg (38%) of Compound 21 and 2.6 mg (4.3%) of Compound 22.

Compound 21:

1H-NMR (CDCl₃) δ ; 2.15 (s, 3H), 3.13 (dd, 1H, J = 4.5, 14.7 Hz), 3.57 (s, 3H), 3.79 (dd, 1H, J = 7.7, 14.7 Hz), 4.09 (s, 3H), 4.46 (s, 2H), 4.53 (d, 1H, J = 6.6 Hz), 4.58 (d, 1H, J = 6.6 Hz), 5.11 (s, 1H), 5.69 (s, 1H), 6.77 (dd, 1H, J = 4.5, 7.7 Hz), 7.10 (d, 1H, J = 8.6 Hz), 7.46 (dd, 1H, J = 1.7, 8.3 Hz), 7.63 (dd, 1H, J = 1.5, 8.5 Hz), 7.92 (d, 1H, J = 8.8 Hz), 7.98 (d, 1H, J = 1.2 Hz), 8.83 (d, 1H, J = 1.5 Hz).

5

FAB-MS (m/z) ; 703 (M+1)⁺

Compound 22:

10 1H-NMR (CDCl₃) δ ; 2.15 (s, 3H), 2.95 (dd, 1H, J = 4.9, 14.7 Hz), 3.54 (s, 3H), 3.55 (s, 3H), 3.60 (dd, 1H, J = 7.6, 14.7 Hz), 4.09 (s, 3H), 4.42 (s, 2H), 4.45 (s, 2H), 4.53 (d, 1H, J = 17.0 Hz), 4.70 (d, 1H, J = 17.0 Hz), 5.19 (br, 1H), 5.32 (br, 1H), 6.78 (dd, 1H, J = 4.9, 7.6 Hz), 7.20 (d, 1H, J = 8.3 Hz), 7.36 (dd, 1H, J = 1.5, 8.3 Hz), 7.61 (dd, 1H, J = 1.7, 8.8 Hz), 7.89 (d, 1H, J = 8.5 Hz), 7.97 (d, 1H, J = 1.5 Hz), 15 8.85 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z) ; 603 (M+1)⁺

Example 22 **Synthesis of Compound 23**

To a solution of 40 mg (0.05 mmol) of Compound F obtained in Reference Example 6 in 3

20 ml of a dichloromethane/diethylamine mixture (2/1) were added 126 mg (0.18 mmol) of bis(triphenylphosphine)palladium(II) chloride and 42 mg (0.22 mmol) of cuprous iodide in a stream of argon, followed by stirring at room temperature for 20 minutes. After addition of 0.16 ml (1.5 mmol) of propargyl alcohol, the mixture was stirred at room temperature for one hour. The reaction mixture was filtered through Celite and the solvent was evaporated under reduced pressure. 25 The residue was purified by silica gel column chromatography (chloroform/methanol = 96/4) to give 456.0 mg (23%) of diacetylated Compound 23.

FAB-MS (m/z) ; 659 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 30.0 mg of diacetylated Compound 23 to give 8.0 mg (33%) of Compound 23.

5 ¹H-NMR (CD₃OD) δ ; 1.90 (s, 1H), 1.93 (s, 1H), 2.14 (dd, 1H, J = 5.0, 14.2 Hz), 2.19 (s, 3H), 3.41 (dd, 1H, J = 7.5, 14.2 Hz), 4.01 (s, 3H), 4.78 (m, 4H), 4.98 (d, 1H, J = 17.6 Hz), 5.03 (d, 1H, J = 17.6 Hz), 7.02 (dd, 1H, J = 5.0, 7.5 Hz), 7.35 (dt, 1H, J = 0.7, 7.8 Hz), 7.49 (m, 2H), 7.63 (d, 1H, J = 8.3 Hz), 7.97 (d, 1H, J = 9.2 Hz), 7.99 (d, 1H, J = 1.1, 8.6 Hz), 9.26 (d, 1H, J = 1.0 Hz).

10 FAB-MS (m/z) ; 576 (M+1)⁺

15 Example 23 Synthesis of Compound 24

Chloroacetyl chloride (0.95 ml, 10 mmol) was added to 5 ml of a suspension of 1.06 g (8 mmol) of aluminum chloride in dichloromethane, and the mixture was stirred at room temperature for 5 minutes. To the mixture was added dropwise 10 ml of a solution of 500 mg (1 mmol) of Compound c (Japanese Published Unexamined Patent Application No. 295588/88) in dichloromethane, followed by stirring at room temperature for 2.5 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the resulting powder was mixed with 1 N hydrochloric acid. The mixture was stirred for one hour and then filtered. The filtrate was purified by silica gel column chromatography (chloroform) to give 270 mg (38%) of Compound 24.

20 ¹H-NMR (CDCl₃) δ ; 1.82 (s, 3H), 2.20 (dd, 1H, J = 5.4, 14.5 Hz), 2.32 (s, 3H), 2.81 (s, 3H), 4.05 (s, 3H), 4.06 (dd, 1H, J = 7.3, 14.5 Hz), 4.87 (dd, 1H, J = 14.1, 15.6 Hz), 5.03 (d, 1H, J = 14.1, 15.6 Hz), 5.45 (m, 2H), 7.03 (dd, 1H, J = 5.1, 7.3 Hz), 7.61 (d, 1H, J = 8.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.21 (dd, 1H, J = 1.7, 8.8 Hz), 8.27 (dd, 1H, J = 1.7, 8.8 Hz), 8.63 (d, 1H, J = 1.5 Hz), 9.87 (d, 1H, J = 1.0 Hz).

25 FAB-MS (m/z) ; 704 (M+1)⁺

Example 24 **Synthesis of Compound 25**

To 1.5 ml of a solution of 36 mg (0.05 mmol) of Compound 24 in chloroform was added 0.025 ml (0.25 mmol) of piperidine, and the mixture was refluxed for 2 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give diacetylated Compound 25.

FAB-MS (m/z) ; 802 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound 10 25 to give 16 mg (42%) of Compound 25.

¹H-NMR (CDCl₃) δ ; 1.42 (m, 4H), 1.56 (m, 8H), 2.07 (dd, 1H, J = 4.8, 14.2 Hz), 2.18 (s, 3H), 2.56 (m, 8H), 3.45 (dd, 1H, J = 7.5, 14.2 Hz), 3.86 (m, 4H), 3.94 (s, 3H), 5.12 (m, 2H), 6.48 (s, 1H), 7.25 (dd, 1H, J = 4.8, 7.5 Hz), 8.02 (d, 2H, J = 9.0 Hz), 15 8.14 (dd, 1H, J = 1.7, 7.1 Hz), 8.16 (dd, 1H, J = 1.7, 7.1 Hz), 8.78 (br, 1H), 8.84 (br, 1H), 9.99 (d, 1H, J = 1.5 Hz).

FAB-MS (m/z) ; 718 (M+1)⁺

Example 25 **Synthesis of Compound 26 and Compound 27**

20 The same procedure as in Example 23 was repeated using 55 mg (0.1 mmol) of Compound c (Japanese Published Unexamined Patent Application No. 295588/88) and 3-chloropropionyl chloride to give 4 mg (6%) of Compound 26 and 26 mg (36%) of Compound 27.

Compound 26:

25 FAB-MS (m/z) ; 642 (M+1)⁺

Compound 27:

FAB-MS (m/z) ; 732 (M+1)⁺

Example 26 **Synthesis of Compound 28**

To 1.5 ml of a solution of 200 mg (0.25 mmol) of Compound 26 in chloroform was added 0.025 ml (0.25 mmol) of piperidine, and the mixture was refluxed for 2 hours. The solvent was 5 evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give diacetylated Compound 28.

FAB-MS (m/z) ; 689 (M+1)⁺

10 The same procedure as in Example 1, Step B was repeated using diacetylated Compound 28 to give 17 mg (11%) of Compound 28.

15 ¹H-NMR (CDCl₃) δ ; 1.48 (br, 2H), 1.65 (t, 4H, J = 5.2 Hz), 2.18 (s, 3H), 2.47 (br, 4H), 2.60 (br, 1H), 3.00(br, 1H), 3.57 (dd, 1H, J = 8.1, 15.4 Hz), 4.07 (s, 3H), 4.15 (d, 1H, J = 15.4 Hz), 4.40 (d, 1H, J = 15.8 Hz), 5.73 (br, 2H), 6.71 (dd, J = 4.6, 7.3 Hz), 7.02 (d, 1H, J = 8.1 Hz), 7.30 (dd, 1H, J = 5.2, 8.1 Hz), 7.43 (dd, 1H, J = 5.2, 8.2 Hz), 7.56 (br, 1H), 7.63 (br, 1H), 7.88 (d, 1H, J = 8.2 Hz), 8.84 (s, 1H).

FAB-MS (m/z) ; 605 (M+1)⁺

20 **Example 27** **Synthesis of Compound 29**

To 1.5 ml of a solution of 60 mg (0.03 mmol) of Compound 27 in chloroform was added 0.025 ml (0.25 mmol) of piperidine, and the mixture was refluxed for 2 hours. The solvent was 25 evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give diacetylated Compound 29.

FAB-MS (m/z) ; 830 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound 29 to give 5.1 mg (8.3%) of Compound 29.

¹H-NMR (DMSO-d₆) δ ; 2.06 (dd, 4H, J = 4.4, 13.9 Hz), 2.17 (s, 3H), 2.49 (br, 12H), 3.29 (br, 4H), 3.44 (dd, 1H, J = 7.3, 13.9 Hz), 3.93 (s, 3H), 5.13 (d, 1H, J = 18.4 Hz), 5.80(d, 1H, J = 18.4 Hz), 6.48(m, 1H), 7.25 (dd, 1H, J = 5.4, 6.3 Hz), 8.00 - 8.16 (m, 4H), 8.62 (br, 1H), 8.77 (br, 1H), 9.96 (s, 1H).

5 FAB-MS (m/z) ; 746 (M+1)⁺

Example 28 **Synthesis of Compound 30**

To 1.5 ml of a solution of 40 mg (0.05 mmol) of Compound 27 in chloroform was added 0.02 ml (0.23 mmol) of morpholine, and the mixture was refluxed for 2 hours. The solvent was 10 evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give diacetylated Compound 30.

FAB-MS (m/z) ; 834 (M+1)⁺

15 The same procedure as in Example 1, Step B was repeated using diacetylated Compound 30 to give 35.5 mg (31%) of Compound 30.

¹H-NMR (DMSO-d₆) δ ; 2.07 (dd, 1H, J = 5.0, 14.7 Hz), 2.16 (s, 3H), 2.45 (m, 8H), 2.77 (br, 4H), 3.30 (m, 4H), 3.44 (dd, 1H, J = 7.5, 14.7Hz), 3.59 (m, 8H), 3.93 (s, 3H), 5.16 (m, 2H), 6.48 (s, 1H), 7.24 (dd, 1H, J = 5.0, 7.5 Hz), 8.02 (dd, 1H, J = 2.2, 20 5.5 Hz), 8.11 (dd, 1H, J = 1.7, 5.8 Hz), 8.14 (dd, 1H, J = 1.7, 5.8 Hz), 8.61 (d, 1H, J = 1.0 Hz), 8.76 (br, 1H), 9.96 (d, 1H, J = 1.2 Hz).

FAB-MS (m/z) ; 750 (M+1)⁺

25 **Example 29** **Synthesis of Compound 31**

To 3 ml of a solution of 100 mg (0.14 mmol) of Compound 24 in chloroform was added 1 ml of morpholine, and the mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 15/1) to give diacetylated Compound 31.

FAB-MS (m/z) ; 806 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using diacetylated Compound
5 31 to give 27 mg (26%) of Compound 31.

10 ¹H-NMR (DMSO-d₆) δ ; 2.06 (dd, 1H, J = 5.0, 14.1 Hz), 2.62 (m, 8H), 3.45(dd, 1H, J = 7.3, 14.1 Hz), 3.63 (m, 8H), 3.91 (m, 2H), 3.98 (m, 2H), 5.13 (d, 2H, J = 7.3 Hz), 6.49 (s, 1H), 7.25 (dd, 1H, J = 5.0, 7.3 Hz), 8.02 (d, 1H, J = 8.9 Hz), 8.13 (dd, 1H, J = 1.7, 9.0 Hz), 8.15 (dd, 1H, J = 1.7, 8.8 Hz), 8.62 (d, 1H, J = 1.7 Hz), 8.77 (s, 1H), 8.78 (d, 1H, J = 1.5 Hz), 10.01 (dd, 1H, J = 0.49, 1.2 Hz)

FAB-MS (m/z) ; 722 (M+1)⁺

Example 30 Synthesis of Compound 32

15 To 3 ml of a solution of 110 mg (0.16 mmol) of Compound 24 in N,N-dimethylformamide was added 54 ml of a 50% aqueous solution of dimethylamine, and the mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give 13.7 mg (14%) of Compound 32.

20 ¹H-NMR (DMSO-d₆) δ ; 2.06 (dd, 1H, J = 4.9, 14.1 Hz), 2.18 (s, 3H), 2.35 (s, 6H), 2.36 (s, 6H), 3.40 (dd, 1H, J = 7.5, 14.1 Hz), 3.87 (m, 2H), 3.93 (m, 2H), 3.94 (s, 3H), 5.13 (m, 2H), 6.47 (s, 1H), 7.25 (dd, 1H, J = 4.9, 7.5 Hz), 8.01 (d, 2H, J = 9.0 Hz), 8.13 (dd, 1H, J = 1.7, 5.6 Hz), 8.16 (dd, 1H, J = 1.7, 5.4 Hz), 8.69 (d, 1H, J = 1.7 Hz), 8.76 (br, 1H), 9.97 (d, 1H, J = 1.2 Hz).

25 FAB-MS (m/z) ; 638 (M+1)⁺

Example 31 Synthesis of Compounds 33a and 33b

To a suspension of 1.06 g (8.0 mmol) of aluminum chloride in 10 ml of methylene chloride was added 0.48 ml (5.0 mmol) of chloroacetyl chloride, and the mixture was stirred at room
30 temperature for 5 minutes. To the mixture was gradually added a solution of 551 mg (1.0 mmol) of

Compound c in 10 ml of methylene chloride, followed by stirring for 2.5 hours. The reaction mixture was then poured into ice-cold water, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the resulting powder was 5 mixed with 1 N hydrochloric acid. The mixture was stirred for one hour, and then insoluble materials were removed by filtration. The filtrate was purified by silica gel column chromatography (chloroform) to give 110 mg (17%) of a mixture of Compounds 33a and 33b.

Compound 33a

10 FAB-MS (m/z); 628, 630 (M+1)⁺

Compound 33b

FAB-MS (m/z); 628, 630 (M+1)⁺

15 **Example 32** Synthesis of Compound 34

To a solution of 64 mg (0.1 mmol) of a mixture of Compounds 33a and 33b in 1.5 ml of N,N-dimethylformamide were added 30 mg (0.2 mmol) of sodium iodide and 1 ml of a 50% aqueous solution of dimethylamine, followed by reflux for 2 hours. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography 20 (chloroform/methanol = 9/1) to give 3.2 g (5.8%) of Compound 34.

25 ¹H-NMR (CDCl₃) δ ; 1.73 (br, 1H), 2.20 (s, 3H), 2.44 (s, 6H), 2.85 (dd, 1H, J = 4.9, 13.7 Hz), 3.61(dd, 1H, J = 7.8, 13.7 Hz), 3.70 (m, 2H), 4.09 (s, 3H), 4.50 (d, 1H, J = 16.6 Hz), 4.70 (d, 1H, J = 16.6 Hz), 5.70 (br, 1H), 6.85 (dd, 1H, J = 4.9, 7.3 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.39 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.83(t, 1H, J = 7.6 Hz), 7.89 (d, 1H, J = 8.3 Hz), 7.90 (d, 1H, J = 7.6 Hz), 9.36 (s, 1H).

FAB-MS (m/z); 553 (M+1)⁺

Example 33 **Synthesis of Compound 35**

To a solution of 63 mg (0.1 mmol) of a mixture of Compounds 33a and 33b in 2 ml of N,N-dimethylformamide was added 90 mg (0.6 mmol) of sodium iodide, and the mixture was then stirred at room temperature for 2 hours. After the solvent was evaporated under reduced pressure, 5 the residue was treated in the same manner as in Example 1, Step B to give 6.8 mg (12%) of Compound 35.

¹H-NMR (DMSO-d₆) δ ; 2.00-2.40 (m, 7H), 2.70-2.80 (m, 4H), 3.40 (br, 1H), 3.94 (s, 3H), 4.22 (br, 2H), 5.02 (d, 1H, J = 18.0 Hz), 5.07 (d, 1H, J = 18.0 Hz), 6.42 (s, 1H), 6.90 (br, 1H), 7.38 (t, 1H, J = 7.5 Hz), 7.51 (dd, 1H, J = 7.5, 8.5 Hz), 7.95 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.7 Hz), 8.08 (d, 1H, J = 7.5 Hz), 8.12 (dd, 1H, J = 1.7, 8.7 Hz), 8.69 (s, 1H), 9.95 (d, 1H, J = 1.4 Hz).
FAB-MS (m/z); 579 (M+1)⁺

15 **Example 34** **Synthesis of Compounds 36a and 36b**

The same procedure as in Example 28 was repeated using 40 mg (0.064 mmol) of a mixture of Compounds 33a and 33b to give 17 mg (40%) of Compound 36a and 10 mg (23%) of Compound 36b.

20 **Compound 36a**

¹H-NMR (CDCl₃) δ ; 1.80 (s, 3H), 2.18 (dd, 1H, J = 5.1, 10.2 Hz), 2.29 (s, 3H), 2.77 (s, 3H), 3.07 (br, 4H), 3.93 (br, 4H), 4.00 (dd, 1H, J = 7.5, 10.1 Hz), 4.07 (s, 3H), 4.35 (br, 2H), 5.38 (d, 2H, J = 5.4 Hz), 6.90 (m, 1H), 7.00 (dd, 1H, J = 5.1, 7.5 Hz), 7.46 (td, 1H, J = 0.5, 7.5 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.57 (td, 1H, J = 1.1, 7.5 Hz), 7.94 (d, 1H, J = 8.5 Hz), 8.07 (d, 1H, J = 7.5 Hz), 8.22 (dd, 1H, J = 1.6, 7.5 Hz), 9.94 (br, 1H).
FAB-MS (m/z); 679 (M+1)⁺

Compound 36b

¹H-NMR (CDCl₃) δ ; 1.80 (s, 3H), 2.15 (dd, 1H, J = 5.1, 12.2 Hz), 2.29 (s, 3H), 2.79 (s, 3H), 2.94 (br, 4H), 3.92 (t, 4H, J = 4.5 Hz), 4.09 (dd, 1H, J = 7.2, 12.2 Hz), 4.02 (s, 3H), 4.35 (br, 2H), 5.38(br, 2H), 7.03 (dd, 1H, J = 5.1, 7.2 Hz), 7.38(br, 1H), 7.56 (br, 1H), 7.95 (d, 1H, J = 8.9 Hz), 8.21 (d, 1H, J = 1.7, 8.9 Hz), 8.78 (br, 1H), 9.21 (d, 1H, J = 8.0 Hz).

5 FAB-MS (m/z); 679 (M+1)⁺

Example 35 Synthesis of Compound 37a

The same procedure as in Example 1, Step B was repeated using 17 mg (0.025 mmol) of
10 Compound 36a to give 3.2 mg (22%) of Compound 37a.

¹H-NMR (DMSO-d₆) δ ; 2.23 (s, 3H), 2.56 (dd, 1H, J = 4.5, 14.7 Hz), 2.72 (br, 4H), 3.43 (dd, 1H, J = 7.6, 14.7 Hz), 3.82 (t, 4H, J = 4.6 Hz), 4.01(br, 1H), 4.11 (s, 3H), 4.86 (d, 1H, J = 16.0 Hz), 4.95 (d, 1H, J = 16.0 Hz), 5.96 (br, 1H), 6.91 (dd, 1H, J = 4.8, 7.4 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.85 (d, 1H, J = 8.6 Hz), 7.92 (d, 1H, J = 7.6 Hz), 8.11 (d, 1H, J = 8.6 Hz), 9.81 (br, 1H).

15 FAB-MS (m/z); 595 (M+1)⁺

20 **Example 36 Synthesis of Compound 37b**

The same procedure as in Example 1, Step B was repeated using 10 mg (0.015 mmol) of Compound 36b to give 1.0 mg (11%) of Compound 37b.

¹H-NMR (DMSO-d₆) δ ; 2.23 (s, 3H), 2.42 (dd, 1H, J = 4.9, 14.5 Hz), 2.64 (br, 4H), 3.35 (dd, 1H, J = 7.6, 14.5 Hz), 3.80 (t, 4H, J = 4.6 Hz), 3.85 (d, 2H, J = 5.3 Hz), 4.12 (s, 3H), 4.29 (br, 1H), 4.80 (d, 1H, J = 16.5 Hz), 4.90 (d, 1H, J = 16.5 Hz), 6.21 (br, 1H), 6.93 (dd, 1H, J = 4.9, 7.4 Hz), 7.30 (br, 1H), 7.49 (m, 2H), 7.83 (d, 1H, J = 8.9 Hz), 8.11 (d, 1H, J = 8.9 Hz), 8.55 (s, 1H), 8.5(s, 1H), 9.20 (d, J = 8.1 Hz, 1H).

FAB-MS (m/z); 595 (M+1)⁺

Example 37 **Synthesis of Compound 38**

The same procedure as in Example 33 was repeated using 162 mg (0.23 mmol) of
5 Compound 24 to give 32 mg (46%) of Compound 38.

10 ¹H-NMR (DMSO-d₆) δ ; 1.95 (s, 3H), 2.30 (m, 9H), 2.65 (m, 8H), 3.45 (dd, 1H, J = 7.1, 14.4 Hz), 3.94 (s, 3H), 4.13 (m, 4H), 5.12 (m, 2H), 6.52 (s, 1H), 7.24 (dd, 1H, J = 4.9, 7.3 Hz), 8.02 (d, 2H, J = 8.8 Hz), 8.29 (m, 2H), 8.72 (s, 1H), 8.76(br, 1H), 9.97 (s, 1H).

FAB-MS (m/z); 689 (M+1)⁺

Example 38 **Synthesis of Compound 39**

To a solution of 211 mg (0.30 mmol) of Compound 24 in 2 ml of N,N-dimethylformamide
15 were added 300 mg (3.0 mmol) of N-methylpiperazine and 90 mg (0.6 mmol) of sodium iodide, and the mixture was stirred at room temperature for 2 hours. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 9/1) to give 190 mg (76%) of Compound 39.

20 FAB-MS (m/z); 832 (M+1)⁺

Example 39 **Synthesis of Compound 40**

The same procedure as in Example 1, Step B was repeated using 17 mg (0.02 mmol) of Compound 39 to give 5.1 mg (34%) of Compound 40.

25

1H-NMR (DMSO-d₆) δ ; 2.06 (dd, J = 4.6, 14.4 Hz, 4H), 2.18 (s, 3H), 2.30 (br, 6H), 2.50 (br, 8H), 2.67 (br, 8H), 3.45 (dd, 1H, J = 7.1, 14.4 Hz), 3.94 (s, 3H), 3.98 (br, 4H), 5.13 (br, 2H), 6.49 (s, 1H), 7.25 (dd, 1H, J = 4.6, 7.1 Hz), 8.02 (d, 2H, J =

8.5 Hz), 8.13 (dd, 1H, J = 1.7, 6.8 Hz), 8.16 (dd, 1H, J = 1.7, 6.8 Hz), 8.78 (br, 2H), 9.99 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 748 (M+1)⁺

5 **Example 40 Synthesis of Compound 41**

To a solution of 50 mg (0.078 mmol) of a mixture of Compounds 33a and 33b in 2 ml of methylene chloride was added 66 mg (0.78 mmol) of sodium ethanethiolate, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated 10 aqueous solution of sodium chloride and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99.8/0.2) to give 17.0 mg (33%) of diacetylated compound 41.

FAB-MS (m/z); 654 (M+1)⁺

15

The same procedure as in Example 1, Step B was repeated using 17 mg (0.026 mmol) of diacetylated Compound 41 to give 5.3 mg (35%) of Compound 41.

¹H-NMR (DMSO-d₆) δ ; 1.23 (t, 3H, J = 7.3 Hz), 2.00 (dd, 1H, J = 4.7, 13.9 Hz), 2.33 (s, 3H), 2.59 (q, 2H, J = 7.3 Hz), 3.42 (dd, 1H, J = 7.3, 13.9 Hz), 3.94 (s, 3H), 4.19 (d, 2H, J = 3.4 Hz), 5.10 (d, 2H, J = 5.1 Hz), 6.44 (br, 1H), 7.18 (dd, 1H, J = 4.9, 7.3 Hz), 8.31 (t, 1H, J = 8.2 Hz), 7.51 (dt, 1H, J = 1.4, 8.3 Hz), 7.92 (d, 1H, J = 8.2 Hz), 8.02 (d, 1H, J = 9.0 Hz), 8.11 (dd, 1H, J = 1.9, 9.0 Hz), 8.63 (d, 1H, J = 1.4 Hz), 8.72 (br, 1H), 9.23 (d, 1H, J = 8.1 Hz).

20

FAB-MS (m/z); 570 (M+1)⁺

Example 41 Synthesis of Compounds 42a and 42b

To a solution of 100 mg (0.16 mmol) of a mixture of Compounds 33a and 33b in 2 ml of N,N-dimethylformamide were added 100 mg (0.9 mmol) of 4-mercaptopyridine and 22 mg (0.16 mmol) of potassium carbonate, followed by stirring at room temperature for 2 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99.8/0.2) to give 70 mg (63%) of a mixture of diacetylated Compounds 42a and 42b.

FAB-MS (m/z); 703 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 70 mg (0.10 mmol) of the mixture of diacetylated compounds to give 3.3 mg (5.3%) of Compound 42a and 5.2 mg (8.4%) of Compound 42b.

Compound 42a

¹H-NMR (DMSO-d₆) δ ; 2.09 (dd, 1H, J = 4.9, 13.9 Hz), 2.19 (s, 3H), 3.44 (dd, 1H, J = 7.3, 13.9 Hz), 3.94 (s, 3H), 4.99 (s, 2H), 5.05 (d, 2H, J = 5.9 Hz), 6.39 (s, 1H), 7.25 (dd, 1H, J = 4.9, 7.3 Hz), 7.39 (t, 1H, J = 8.6 Hz), 7.41 (d, 1H, J = 6.4 Hz), 7.52 (t, 1H, J = 8.6 Hz), 7.96 (d, 1H, J = 8.6 Hz), 8.071 (d, 1H, J = 8.8 Hz), 8.074 (d, 1H, J = 8.6 Hz), 8.25 (dd, 1H, J = 1.7, 8.8 Hz), 8.40 (d, 2H, J = 6.4 Hz), 8.71 (s, 1H), 9.98 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z); 619 (M+1)⁺

Compound 42b

¹H-NMR (CDCl₃) δ ; 2.24 (s, 3H), 2.39 (dd, 1H, J = 5.1, 14.4 Hz), 3.36 (dd, 1H, J = 7.3, 14.4 Hz), 4.12 (s, 3H), 4.46 (d, 2H, J = 3.4 Hz), 4.83 (d, 1H, J = 16.4 Hz), 4.93

(d, 1H, $J = 16.4$ Hz), 6.15 (s, 1H), 6.93 (dd, 1H, $J = 4.9, 7.3$ Hz), 7.11-7.29 (br, 5H), 7.22-7.58 (br, 2H), 7.86 (d, 1H, $J = 8.3$ Hz), 8.04 (d, 1H, $J = 8.3$ Hz), 8.48 (d, 1H, $J = 2.7$ Hz), 8.51 (s, 1H), 9.22 (d, 1H, $J = 8.3$ Hz).

FAB-MS (m/z); 619 (M+1)⁺

5

Example 42 **Synthesis of Compound 43**

To a solution of 211 mg (0.30 mmol) of Compound 24 in 4 ml of chloroform/methanol (3/1) was added 56 mg (0.80 mmol) of sodium methanethiolate, followed by stirring at room 10 temperature for 30 minutes. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 125 mg (57%) of diacetylated Compound 43.

15 FAB-MS (m/z); 728 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 125 mg (0.017 mmol) of diacetylated Compound 43 to give 48 mg (44%) of Compound 43.

20 ¹H-NMR (DMSO-d₆) δ ; 2.07 (dd, 1H, $J = 4.9, 14.4$ Hz), 2.13 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 3.45 (dd, 1H, $J = 7.3, 14.4$ Hz), 3.94 (s, 3H), 4.04 (s, 2H), 4.17 (d, 2H, $J = 2.9$ Hz), 5.14 (d, 2H, $J = 4.6$ Hz), 6.50 (br, 1H), 7.26 (dd, 1H, $J = 4.9, 7.3$ Hz), 8.03 (d, 1H, $J = 8.8$ Hz), 8.04 (d, 1H, $J = 8.8$ Hz), 8.13 (dd, 1H, $J = 2.0, 8.8$ Hz), 8.17 (dd, 1H, $J = 2.0, 8.8$ Hz), 8.65 (d, 1H, $J = 1.7$ Hz), 8.78 (br, 1H), 9.93 (d, 1H, $J = 1.5$ Hz).

25 FAB-MS (m/z); 644 (M+1)⁺

Example 43 Synthesis of Compound 44

To a solution of 50 mg (0.07 mmol) of Compound 24 in 2 ml of methylene chloride was added 59 mg (0.7 mmol) of sodium ethanethiolate, followed by stirring at room temperature for 3 hours. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99.8/0.2) to give 19.7 mg (36%) of diacetylated Compound 44.

FAB-MS (m/z); 756 (M+1)⁺

10 The same procedure as in Example 1, Step B was repeated using 19 mg (0.025 mmol) of diacetylated Compound 44 to give 12.5 mg (67%) of Compound 44.

15 ¹H-NMR (DMSO-d₆) δ ; 1.22 (t, 3H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 2.08 (dd, 1H, J = 4.9, 13.9 Hz), 2.18 (s, 3H), 2.60 (br, 4H), 3.45 (dd, 1H, J = 7.3, 13.9 Hz), 3.94 (s, 3H), 4.07 (br, 2H), 4.19 (d, 2H, J = 4.2 Hz), 5.14 (br, 2H), 6.49 (br, 1H), 7.26 (dd, 1H, J = 4.9, 7.3 Hz), 8.03 (d, 1H, J = 9.0 Hz), 8.04 (dd, 1H, J = 8.8 Hz), 8.13 (dd, 1H, J = 1.7, 9.0 Hz), 8.16 (dd, 1H, J = 2.0, 8.8 Hz), 8.65 (d, 1H, J = 1.7 Hz), 8.79 (br, 1H), 9.94 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 672 (M+1)⁺

20

Example 44 Synthesis of Compound 45

To a solution of 100 mg (0.16 mmol) of Compound 24 in 3.5 ml of N,N-dimethylformamide/methanol (6/1) were added 0.038 ml (0.32 mmol) of propanethiol and 44 mg (0.32 mmol) of potassium carbonate, followed by stirring at room temperature for 2 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 95/5) to give 32 mg (23%) of Compound 45.

¹H-NMR (DMSO-d₆) δ ; 0.93 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz), 1.59 (qt, 2H, J = 7.2, 7.3 Hz), 1.60 (tq, 2H, J = 7.3, 7.2 Hz), 2.07 (dd, 1H, J = 5.0, 13.1 Hz), 2.18 (s, 3H), 2.57 (t, 2H, J = 7.2 Hz), 2.58 (t, 2H, J = 7.2 Hz), 3.45 (dd, 1H, J = 7.6, 13.1 Hz), 3.94 (s, 3H), 4.04 (s, 2H), 4.15 (d, 2H, J = 5.1 Hz), 5.14 (d, 2H, J = 8.0 Hz), 6.50 (br, 1H), 7.26 (dd, 1H, J = 5.0, 7.3 Hz), 8.03 (d, 1H, J = 8.9 Hz), 8.04 (d, 1H, J = 8.7 Hz), 8.12 (dd, 1H, J = 1.7, 8.9 Hz), 8.16 (dd, J = 1.7, 8.7 Hz), 8.65 (d, 1H, J = 1.6 Hz), 8.80 (br, 1H), 9.93 (d, 1H, J = 1.6 Hz).

FAB-MS (m/z); 700 (M+1)⁺

10 **Example 45 Synthesis of Compound 46**

To a solution of 70 mg (0.10 mmol) of Compound 24 in 3.5 ml of N,N-dimethylformamide/methanol (6/1) were added 23 mg (0.30 mmol) of 2-hydroxyethanethiol and 50 mg (0.36 mmol) of potassium carbonate, followed by stirring at room temperature for 1 day. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. 15 The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 40 mg (51%) of diacetylated Compound 46.

FAB-MS (m/z); 784 (M+1)⁺

20

The same procedure as in Example 1, Step B was repeated using 40 mg (0.051 mmol) of diacetylated Compound 46 to give 20 mg (56%) of Compound 46.

¹H-NMR (DMSO-d₆) δ ; 2.07 (dd, 1H, J = 5.1, 14.3 Hz), 2.18 (s, 3H), 2.67 (br, 4H), 3.45 (dd, 1H, J = 7.6, 14.3 Hz), 3.59 (br, 4H), 3.94 (s, 3H), 4.10 (s, 2H), 4.22 (d, 2H, J = 5.9 Hz), 4.82 (br, 2H), 6.50 (s, 1H), 7.26 (dd, 1H, 5.1, 7.6 Hz), 8.04 (d, 1H, J = 9.0 Hz), 8.05 (d, 1H, J = 8.7 Hz), 8.13 (dd, 1H, J = 1.7, 9.0 Hz), 8.16 (dd, 1H, J = 1.7, 8.7 Hz), 8.65 (d, 1H, J = 1.7 Hz), 8.81 (s, 1H), 9.93 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 700 (M+1)⁺

Example 46 Synthesis of Compound 47

To a solution of 100 mg (0.16 mmol) of Compound 24 in 2 ml of N,N-dimethylformamide
5 were added 100 mg (0.9 mmol) of 4-mercaptopyridine and 44 mg (0.32 mmol) of potassium
carbonate, followed by stirring at room temperature for 2 hours. The reaction mixture was poured
into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with
a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent
was evaporated under reduced pressure, the residue was purified by silica gel column
10 chromatography (chloroform/methanol = 99.8/0.2) to give 67 mg (63%) of diacetylated Compound
47.

FAB-MS (m/z); 854 (M+1)⁺

15 The same procedure as in Example 1, Step B was repeated using 67 mg (0.10 mmol) of
diacetylated Compound 47 to give 45 mg (58%) of Compound 47.

¹H-NMR (DMSO-d₆) δ ; 2.08 (dd, 1H, J = 4.8, 14.3 Hz), 2.19 (s, 3H), 3.47 (dd, 1H, J =
7.5, 14.3 Hz), 3.95 (s, 3H), 4.97 (s, 2H), 5.12 (d, 2H, J = 4.9 Hz), 5.18 (s, 2H),
20 6.53 (s, 1H), 7.30 (dd, 1H, J = 4.8, 7.5 Hz), 7.37 (br, 4H), 8.07 (d, 1H, J = 9.0
Hz), 8.10 (d, 1H, J = 8.7 Hz), 8.19 (dd, 1H, J = 1.7, 9.0 Hz), 8.29 (dd, 1H, J = 1.8,
8.7 Hz), 8.21-8.57 (br, 4H), 8.76 (d, 1H, J = 1.7 Hz), 8.86 (s, 1H), 9.99 (d, 1H, J
= 1.8 Hz).

FAB-MS (m/z); 770 (M+1)⁺

Example 47 **Synthesis of Compound 48**

To a solution of 160 mg (0.26 mmol) of Compound 24 in 2 ml of N,N-dimethylformamide were added 290 mg (2.6 mmol) of 2-mercaptopypyridine and 83 mg (0.6 mmol) of potassium carbonate, followed by stirring at room temperature for 2 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99.8/0.2) to give 123 mg (55%) of diacetylated Compound 48.

FAB-MS (m/z); 854 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 20 mg (0.023 mmol) of diacetylated Compound 48 to give 10 mg (53%) of Compound 48.

¹H-NMR (DMSO-d₆) δ ; 2.09 (dd, 1H, J = 4.8, 14.2 Hz), 2.19 (s, 3H), 3.47 (dd, 1H, J = 7.3, 14.2 Hz), 3.95 (s, 3H), 4.94 (s, 2H), 5.02 (d, 2H, J = 3.4 Hz), 5.10 (d, 2H, J = 7.7 Hz), 6.52 (s, 1H), 7.01-7.27 (br, 5H), 7.41 (d, 2H, J = 8.0 Hz), 7.66 (dt, 2H, J = 1.1, 8.0 Hz), 8.06 (d, 1H, J = 8.8 Hz), 8.29 (d, 1H, J = 8.8 Hz), 8.37 (ddd, 2H, J = 0.8, 4.1, 8.0 Hz), 8.72 (s, 1H), 8.81 (s, 1H), 10.02 (s, 1H).

FAB-MS (m/z); 770 (M+1)⁺

Example 48 **Synthesis of Compound 49**

To a solution of 140 mg (0.10 mmol) of Compound 24 in 3 ml of N,N-dimethylformamide were added 70 mg (0.60 mmol) of 2-mercaptopypyridine and 50 mg (0.36 mmol) of potassium carbonate, followed by stirring at room temperature for 3 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column

chromatography (chloroform/methanol = 95/5) to give 17 mg (16%) of diacetylated Compound 49 and 15 mg (18%) of monoacetylated Compound 49.

Diacetylated Compound FAB-MS (m/z); 856 (M+1)⁺

5 Monoacetylated Compound FAB-MS (m/z); 814 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 17 mg (0.020 mmol) of diacetylated Compound 49 to give 8.7 mg (56%) of Compound 49.

10 ¹H-NMR (DMSO-d₆) δ ; 2.09 (dd, 1H, J = 4.9, 14.0 Hz), 2.19 (s, 3H), 3.30 (br, 1H), 3.95 (s, 3H), 4.96 (s, 2H), 5.03 (s, 2H), 5.15 (d, 2H, J = 2.7 Hz), 6.52 (s, 1H), 7.28-7.30 (m, 3H), 8.08 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 8.8 Hz), 8.19 (dd, 1H, J = 1.7, 8.8 Hz), 8.23 (dd, 1H, J = 1.7, 8.8 Hz), 8.59 (d, 2H, J = 4.9 Hz), 8.61 (d, 2H, J = 4.9 Hz), 8.74 (d, 1H, J = 1.7 Hz), 8.80 (br, 1H), 10.0 (d, 1H, J = 1.7 Hz).

15 FAB-MS (m/z); 772 (M+1)⁺

Example 49 **Synthesis of Compound 50**

To a solution of 105 mg (0.15 mmol) of Compound 24 in 1.8 ml of N,N-dimethylformamide/methanol (5/1) were added 38 mg (0.30 mmol) of 4-hydroxymercaptobenzene and 50 mg (0.36 mmol) of potassium carbonate, followed by stirring at room temperature for 12 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 9/1) to give 76 mg (63%) of Compound 50.

¹H-NMR (DMSO-d₆) δ ; 2.08 (s, 3H), 2.09 (dd, 1H, J = 2.7, 7.6 Hz), 3.45 (dd, 1H, J = 7.6, 14.2 Hz), 3.94 (s, 3H), 4.44 (br, 2H), 4.56 (d, 2H, J = 5.1 Hz), 5.11 (d, 2H, J = 4.4 Hz) 6.50 (s, 1H), 6.73 (td, 4H, J = 2.2, 8.9 Hz), 7.27 (m, 3H), 8.02 (d, 1H, J

= 8.9 Hz), 8.04 (d, 1H, J = 1.7, 8.9 Hz), 8.09 (dd, 1H, J = 1.7, 8.9 Hz), 8.14 (dd, 1H, J = 1.9, 8.9 Hz), 8.61 (d, 1H, J = 1.7 Hz), 8.77 (s, 1H), 9.58 (s, 2H), 9.92 (d, 1H, J = 1.4 Hz).

FAB-MS (m/z); 800 (M+1)⁺

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Example 50 Synthesis of Compound 51

To a solution of 70 mg (0.10 mmol) of Compound 24 in 2 ml of N,N-dimethylformamide were added 25 mg (0.21 mmol) of 2-mercaptopthiazoline and 28 mg (0.20 mmol) of potassium carbonate, followed by stirring at room temperature for 1 hour. To the mixture was added a 10 solution of sodium methoxide in methanol, followed by stirring for 30 minutes. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 9/1) to give 30 mg (38%) of Compound 51.

15

¹H-NMR (DMSO-d₆) δ ; 2.07 (br, 1H), 2.18 (s, 3H), 3.48 (br, 5H), 3.95 (s, 3H), 4.11 (t, 2H, J = 8.0 Hz), 4.15 (t, 2H, J = 8.0 Hz), 4.96 (s, 2H), 5.02 (s, 2H), 5.16 (d, 2H, J = 2.7 Hz), 6.51 (s, 1H), 7.27 (dd, 1H, J = 4.9, 7.2 Hz), 8.06 (d, 2H, J = 8.8 Hz), 8.13 (dd, 1H, J = 1.7, 8.8 Hz), 8.17 (dd, 1H, J = 1.7, 8.8 Hz), 8.68 (d, 1H, J = 1.7 Hz), 8.82 (s, 1H), 9.96 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 786 (M+1)⁺

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Example 51 **Synthesis of Compound 52**

To a solution of 160 mg (0.26 mmol) of Compound 24 in 2 ml of N,N-dimethylformamide were added 290 mg (2.6 mmol) of 5-mercaptop-1-methyltetrazole and 83 mg (0.6 mmol) of 5 potassium carbonate, followed by stirring at room temperature for 2 hours. The reaction mixture was poured into ice-cold water, and precipitates were removed by filtration. The filtrate was purified by silica gel column chromatography (chloroform/methanol = 9/1) to give 50 mg (23%) of diacetylated Compound 52.

10 FAB-MS (m/z); 864 (M+1)⁺

The same procedure as in Example 1, Step B was repeated using 50 mg (0.058 mmol) of diacetylated Compound 52 to give 20 mg (44%) of Compound 52.

15 ¹H-NMR (DMSO-d₆) δ ; 2.10 (dd, 1H, J = 4.8, 14.2 Hz), 2.19 (s, 3H), 3.47 (dd, 1H, J = 7.5, 14.2 Hz), 3.95 (s, 3H), 4.05 (s, 6H), 5.20 (s, 2H), 5.24 (s, 2H), 5.33 (s, 2H), 6.54 (s, 1H), 7.30 (dd, 1H, J = 4.8, 7.5 Hz), 8.08 (d, 1H, J = 9.0 Hz), 8.10 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 9.0 Hz), 8.21 (d, 1H, J = 9.0 Hz), 8.72 (s, 1H), 8.84 (s, 1H), 9.98 (s, 1H).

20 FAB-MS (m/z); 780 (M+1)⁺

Example 52 **Synthesis of Compound 53**

To a solution of 211 mg (0.30 mmol) of Compound 27 in 5 ml of chloroform/methanol (1/1) was added 56 mg (0.80 mmol) of sodium methanethiolate, followed by stirring at room 25 temperature for 3 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 52 mg (26%) of Compound 53.

¹H-NMR (DMSO-d₆) δ ; 2.07 (dd, 1H, J = 4.9, 14.1 Hz), 2.16 (s, 3H), 2.17 (s, 3H), 2.18 (s, 3H), 2.87 (dd, 1H, J = 7.4, 14.1 Hz), 2.88 (t, 2H, J = 7.1 Hz), 2.89 (t, 2H, J = 7.1 Hz), 3.44 (t, 2H, J = 7.1 Hz), 3.53 (t, 2H, J = 7.1 Hz), 3.94 (s, 3H), 5.16 (d, 2H, J = 3.9 Hz), 6.49 (s, 1H), 7.25 (dd, 1H, J = 4.9, 7.4 Hz), 8.03 (d, 1H, J = 9.0 Hz), 8.04 (d, 1H, J = 8.8 Hz), 8.12 (dd, 1H, J = 1.7, 9.0 Hz), 8.14 (dd, 1H, J = 1.7, 8.8 Hz), 8.61 (d, 1H, J = 1.7 Hz), 8.77 (br, 1H), 9.96 (d, 1H, J = 1.5 Hz).

5 FAB-MS (m/z); 672 (M+1)⁺

Example 53 **Synthesis of Compound 54**

10 To a solution of 110 mg (0.2 mmol) of Compound c in 5 ml of methylene chloride was added 0.16 ml (2 mmol) of acryloyl chloride, followed by stirring at room temperature for 5 minutes. To the mixture was gradually added 0.40 g (3 mmol) of aluminum chloride, followed by stirring for 2.5 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium 15 chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give diacetylated Compound 54. The same procedure as in Example 1, Step B was repeated using the diacetylated Compound 54 to give 32 mg (25%) of Compound 54.

¹H-NMR (DMSO-d₆) δ ; 2.07 (dd, 1H, J = 4.9, 14.4 Hz), 2.17 (s, 3H), 2.50 (s, 6H), 3.37 (t, 2H, J = 6.2 Hz), 3.45 (br, 1H), 3.46 (t, 2H, J = 6.2 Hz), 3.80 (dt, 4H, J = 1.2, 6.2 Hz), 3.94 (s, 3H), 5.16 (d, 2H, J = 3.9 Hz), 6.49 (s, 1H), 7.25 (dd, 1H, J = 4.9, 7.2 Hz), 8.03 (dd, 2H, J = 1.9, 9.0 Hz), 8.11 (dd, 1H, J = 1.5, 9.0 Hz), 8.13 (dd, 1H, J = 1.5, 9.0 Hz), 8.62 (d, 1H, J = 1.6 Hz), 8.77 (br, 1H), 9.96 (d, 1H, J = 1.7 Hz).

25 FAB-MS (m/z); 640 (M+1)⁺

Example 54 **Synthesis of Compound 55**

To a solution of 126 mg (0.2 mmol) of Compound A in 5 ml of methylene chloride was added 0.21 ml (2.0 mmol) of n-butyryl chloride, followed by stirring at room temperature for 5

minutes. To the mixture was gradually added 0.40 g (3 mmol) of aluminum chloride, followed by stirring for 2.5 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 5 diacetylated Compound 55. The same procedure as in Example 1, Step B was repeated using the diacetylated compound to give 21 mg (25%) of Compound 55.

10 ¹H-NMR (DMSO-d₆) δ ; 1.01 (t, 2H, J = 7.3 Hz), 1.74 (tq, 2H, J = 7.1, 7.3 Hz), 2.01 (dd, 1H, J = 4.9, 14.2 Hz), 2.17 (s, 3H), 2.19 (t, 2H, J = 7.1 Hz), 3.41 (dd, 1H, J = 7.3, 14.2 Hz), 3.93 (s, 3H), 5.13 (d, 2H, J = 3.9 Hz), 6.45 (s, 1H), 7.19 (dd, 1H, J = 4.9, 7.3 Hz), 7.64 (dd, 1H, J = 2.0, 8.8 Hz), 7.95 (d, 1H, J = 8.8 Hz), 8.02 (d, 1H, J = 9.0 Hz), 8.12 (dd, 1H, J = 1.7, 9.0 Hz), 8.59 (d, 1H, J = 1.5 Hz), 8.78 (s, 1H), 9.41 (d, 1H, J = 1.7 Hz).

15 FAB-MS (m/z); 616, 618 (M+1)⁺

Example 55 Synthesis of Compound 56

20 To a solution of 82 mg (0.15 mmol) of Compound c in 2 ml of methylene chloride was added 0.18 ml (1.5 mmol) of valeroyl chloride, followed by stirring at room temperature for 5 minutes. To the mixture was gradually added 0.27 g (2.0 mmol) of aluminum chloride, followed by stirring for 3 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99/1) to give 59 mg (45%) of Compound 56.

25

¹H-NMR (CDCl₃) δ ; 1.01 (t, 3H, J = 7.6 Hz), 1.02 (t, 3H, J = 7.6 Hz), 1.51 (br, 4H), 1.80 (s, 3H), 1.82 (br, 4H), 2.17 (dd, 1H, J = 5.1, 14.7 Hz), 2.31 (s, 3H), 2.77 (s, 3H), 3.15 (br, 4H), 4.02 (dd, 1H, J = 7.4, 14.7 Hz), 4.03 (s, 3H), 5.38 (d, 2H, J = 2.32 Hz), 6.99 (dd, 1H, J = 5.1, 7.4 Hz), 7.52 (d, 1H, J = 8.7 Hz), 7.96 (d, 1H, J =

8.8 Hz), 8.18 (dd, 1H, J = 1.7, 8.7 Hz), 8.19 (dd, 1H, J = 1.8, 8.8 Hz), 8.57 (d, 1H, J = 1.5 Hz), 9.82 (d, 1H, J = 1.6 Hz).

FAB-MS (m/z); 720 (M+1)⁺

5 **Example 56 Synthesis of Compound 57**

To a solution of 127 mg (0.2 mmol) of Compound g in 3.0 ml of chloroform were added 48 mg (0.1 mmol) of tetrabutylammonium bromide and 1 ml of methanol, followed by reflux for 5 hours. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium 10 chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99/1) to give 21 mg (13%) of Compound 57.

15 ¹H-NMR (CDCl₃) δ ; 1.82 (s, 3H), 2.18 (dd, 1H, J = 5.1, 14.5 Hz), 2.33 (s, 3H), 2.77 (s, 3H), 4.04 (s, 3H), 4.05 (dd, 1H, J = 7.3, 14.5 Hz), 4.62 (d, 2H, J = 4.9 Hz), 4.76 (d, 2H, J = 1.0 Hz), 5.41 (d, 2H, J = 1.5 Hz), 7.02 (dd, 1H, J = 5.1, 7.3 Hz), 7.58 (d, 1H, J = 8.8 Hz), 8.01 (d, 1H, J = 8.8 Hz), 8.23 (dd, 1H, J = 1.7, 8.8 Hz), 8.25 (dd, 1H, J = 1.7, 8.8 Hz), 8.64 (d, 1H, J = 1.7 Hz), 9.88 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 794 , 796, 798(M+1)⁺

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Example 57 Synthesis of Compound 58

To a solution of 105 mg (0.18 mmol) of Compound d in 3 ml of methanol/chloroform (1/1) was added 6.8 mg (0.18 mmol) of sodium borohydride, followed by stirring under ice cooling for 30 minutes. The reaction mixture was then poured into ice-cold water, followed by extraction with 25 chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99/1) to give 85 mg (81%) of Compound 58.

FAB-MS (m/z); 596 (M+1)⁺

Example 58 Synthesis of Compound 59

The same procedure as in Example 1, Step B was repeated using the product obtained by repeating the same procedure as in Example 57 using 73 mg (0.1 mmol) of Compound 27 to give 37 mg (65%) of Compound 59.

¹H-NMR (DMSO-d₆) δ ; 1.98 (br, 1H), 2.10 (br, 2H), 2.14 (s, 3H), 2.22 (br, 2H), 3.37 (dd, 1H, J = 7.3, 13.9 Hz), 3.65 (br, 2H), 3.80 (br, 2H), 3.93 (s, 3H), 4.85 (br, 2H), 5.10 (br, 2H), 5.43 (br, 1H), 5.48 (br, 1H), 6.31 (s, 1H), 7.12 (dd, 1H, J = 6.8, 7.3 Hz), 7.48 (br, 2H), 7.85 (br, 2H), 7.96 (d, 0.5 H, J = 1.5 Hz), 7.97 (d, 0.5 H, J = 1.5 Hz), 8.59 (s, 1H), 9.16 (d, 0.5 H, J = 1.5 Hz), 9.19 (d, 0.5 H, J = 1.5 Hz).

FAB-MS (m/z); 652 (M+1)⁺

Example 59 Synthesis of Compound 60

The same procedure as in Example 57 was repeated using 100 mg (0.12 mmol) of Compound 40 to give 47 mg (51%) of Compound 60.

20 FAB-MS (m/z); 640 (M+1)⁺

Example 60 Synthesis of Compound 61

The same procedure as in Example 20 was repeated using 68 mg (0.10 mmol) of Compound H to give 8.7 mg (16%) of Compound 61.

¹H-NMR (DMSO-d₆) δ : 2.18 (s, 3H), 2.46 (s, 6H), 2.83 (dd, 1H, J = 4.9, 14.4 Hz), 3.52 (dd, 1H, J = 7.3, 14.4 Hz), 3.56 (s, 2H), 4.08 (s, 3H), 4.71 (d, 1H, J = 15.9 Hz), 4.80 (d, 1H, J = 15.9 Hz), 4.90 (br, 1H), 5.46 (br, 1H), 6.80 (dd, 1H, J = 4.9, 7.3

Hz), 7.24 (d, 1H, J = 8.3 Hz), 7.41 (br, 2H), 7.53 (dt, 1H, J = 1.1, 7.1 Hz), 7.93 (br, 2H), 9.06 (s, 1H).

FAB-MS (m/z); 549 (M+1)⁺

5 **Example 61 Synthesis of Compound 62**

In a 30-ml two-necked flask were placed 12.6 mg (0.018 mmol) of bis(triphenylphosphine) palladium (II) chloride and 4.2 mg (0.022 mmol) of CuI, and the atmosphere was replaced with argon. To the mixture was added a solution of 40 mg (0.059 mmol) of Compound I in 3 ml of methylene chloride/diethylamine (2/1), followed by stirring at room temperature for 20 minutes.

10 To the mixture was added 0.16 ml (1.5 mmol) of N-methyl-N-propargylbenzylamine, followed by stirring at room temperature for 3 hours. After insoluble materials were removed by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methanol/chloroform = 1/25) to give 12.3 mg (Z-form, 30%) of Compound 62.

15 ¹H-NMR (DMSO-d₆) δ ; 2.02 (dd, 1H, J = 4.9, 13.7 Hz), 2.14 (s, 3H), 2.34 (s, 3H), 3.28 (d, 2H, J = 9.5 Hz), 3.40 (dd, 1H, J = 7.3, 13.7 Hz), 3.57 (s, 2H), 3.66 (s, 2H), 3.93 (s, 3H), 5.05 (d, 1H, J = 18.2 Hz), 5.10 (d, 1H, J = 18.2 Hz), 6.42 (s, 1H), 7.17 (dd, 1H, J = 4.9, 7.3), 7.29 (br, 1H), 7.37 (br, 4H), 7.58 (d, 1H, J = 1.5, 8.8 Hz), 7.63 (d, 1H, J = 2.2, 8.8 Hz), 7.94 (d, 2H, J = 8.8 Hz), 8.11 (d, 1H, J = 1.5 Hz), 8.74 (s, 1H), 9.40 (d, 1H, J = 2.2 Hz).

FAB-MS (m/z); 704, 706 (M+1)⁺

Example 62 Synthesis of Compound 63

To a solution of 71.4 mg (0.1 mmol) of diacetylated Compound 20 in 3 ml of methanol was added 25 mg of 10% Pd/C, followed by reflux in a hydrogen atmosphere for 1 hour. Insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give 23.0 mg (Z-form, 33%) of Compound 63.

FAB-MS (m/z); 718 (M+1)⁺

Example 63 **Synthesis of Compound 64**

The same procedure as in Example 1, Step B was repeated using 23 mg (0.033 mmol) of
5 Compound 63 to give 8.7 mg (41%) of Compound 64.

¹H-NMR (CD₃OD) δ ; 2.11 (dd, 1H, J = 5.0, 14.1 Hz), 2.21 (s, 3H), 2.34 (s, 6H), 2.44 (s,
6H), 3.43 (dd, 1H, J = 7.7, 14.4 Hz), 3.55 (dd, 2H, J = 1.5, 6.5 Hz), 3.67 (dd, 2H, J
= 1.5, 6.5 Hz), 4.02 (s, 3H), 5.03 (d, 2H, J = 5.8 Hz), 5.74 (dt, 1H, J = 6.5, 11.7
10 Hz), 5.80 (s, 1H), 6.87 (d, 1H, J = 11.7 Hz), 6.88 (d, 1H, J = 11.7 Hz), 7.05 (dd,
1H, J = 5.0, 7.7 Hz), 7.20-7.58 (m, 2H), 7.68 (d, 1H, J = 8.4 Hz), 7.86 (s, 1H),
7.95 (d, 1H, J = 8.8 Hz), 9.16 (s, 1H).

FAB-MS (m/z); 634 (M+1)⁺

15 **Example 64** **Synthesis of Compound 65**

To a solution of 1.16 g (0.64 mmol) of Compound e in 100 ml of acetonitrile was added
823 mg (2.4 mmol) of triphenylphosphine hydrobromide, followed by stirring at 80 °C for 1 hour.
To the mixture was added ethyl acetate, and the precipitated phosphonium salt was collected by
filtration, and dried under reduced pressure to give 1.22 g (67%) of crude phosphonium salt. To a
20 solution of 91 mg (0.1 mmol) of the phosphonium salt in 3 ml of methylene chloride were added
16.5 mg (1.3 mmol) of potassium carbonate and 3.0 mg (0.011 mmol) of 18-crown-6, followed by
stirring at room temperature for 30 minutes. To the mixture was added 2.3 ml (5.0 mmol) of
propionaldehyde, followed by stirring at room temperature for 4 days. The reaction mixture was then
poured into a saturated aqueous solution of ammonium chloride, followed by extraction with
25 chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and
dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue
was purified by silica gel column chromatography (chloroform/methanol = 200/1) to give 22.6 mg
(E/Z = 1/1, 37%) of Compound 65.

FAB-MS (m/s); 606 (M+1)⁺

Example 65 **Synthesis of Compound 66**

5 The same procedure as in Example 1, Step B was repeated using 22.6 mg (0.037 mmol) of Compound 65 to give 13.1 mg (E/Z = 1/1, 68%) of Compound 66.

FAB-MS (m/s); 522 (M+1)⁺

Example 66 **Synthesis of Compound 67**

10 The same procedure as in Example 64 was repeated using 450 mg (0.64 mmol) of Compound K to give 367 mg (E/Z = 1/1, 78%) of Compound 67.

FAB-MS (m/s); 732 (m+1)⁺

15 **Example 67** **Synthesis of Compound 68**

To a solution of 120 mg (0.02 mmol) of Compound f in 100 ml of acetonitrile was added 823 mg (2.4 mmol) of triphenylphosphine hydrobromide, followed by stirring at 80°C for 1 hour. To the mixture was then added ethyl acetate, and the precipitated phosphonium salt was collected by filtration, and dried under reduced pressure to give crude phosphonium salt. To a solution of the phosphonium salt in 3 ml of methylene chloride were added 26 mg (0.2 mmol) of potassium-t-butoxide and 6.0 mg (0.022 mmol) of 18-crown-6, followed by stirring at room temperature for 30 minutes. To the mixture was added 0.12 ml (0.25 mmol) of propionaldehyde, followed by stirring at room temperature for 4 days. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give diacetylated Compound 68. The same procedure as in Example 1, Step B was repeated using the diacetylated compound to give 17.0 mg (mixture of E and Z, 13%) of Compound 68.

FAB-MS (m/s); 576 (M+1)⁺

Example 68 **Synthesis of Compound 69**

To a solution of 211 mg (0.3 mmol) of Compound 24 in 2 ml of trifluoroacetic acid was
5 added 0.19 ml (1.5 mmol) of triethylsilane, followed by stirring under ice cooling for 2 hours. The
reaction mixture was the poured into ice-cold water, and the resulting precipitates were collected by
filtration, and washed with hexane. The product was then purified by silica gel column
chromatography (chloroform) to give 150 mg (73%) of diacetylated Compound 69. The same
procedure as in Example 1, Step B was repeated using 68 mg (0.1 mmol) of diacetylated Compound
10 69 to give 48 mg (81%) of Compound 69.

¹H-NMR (DMSO-d₆) δ ; 1.98 (dd, 1H, J = 3.8, 5.5 Hz), 2.13 (s, 3H), 3.24 (m, 5H), 3.92
(s, 3H), 3.93 (t, 2H, J = 7.2 Hz), 3.97 (t, 2H, 7.5 Hz), 5.01 (br, 2H), 6.30 (s, 1H),
15 7.11 (dd, 1H, J = 3.8, 7.2 Hz), 7.40 (dd, 1H, J = 1.5, 8.3 Hz), 7.42 (dd, 1H, J =
1.5, 8.3 Hz), 7.84 (d, 1H, J = 8.3 Hz), 7.86 (d, 1H, 8.3 Hz), 7.97 (d, 1H, J = 1.2
Hz), 8.63 (br, 1H), 9.08 (d, 1H, J = 1.2 Hz).

FAB-MS (m/s); 592, 594, 596(M+1)⁺

Example 69 **Synthesis of Compounds 70a, 70b and 70c**

To a solution of 679 mg (1.2 mmol) of Compound 69 in 10 ml of N,N-dimethylformamide
20 was added 380 mg (23 mmol) of potassium iodide, followed by stirring at 90 °C for 3 hours. The
reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol
(9/1). The extract was washed with a saturated aqueous solution of sodium chloride and then dried
over sodium sulfate. After evaporation under reduced pressure, the residue was purified by silica
25 gel column chromatography (chloroform) to give 300 mg (67%) of Compound 70a, 89 mg (15%) of
Compound 70b, and 42 mg (5%) of Compound 70c.

Compound 70a

¹H-NMR (CDCl₃) δ; 2.20 (s, 3H), 2.47 (dd, 1H, J = 4.8, 8.3 Hz), 3.40 (br, 9H), 4.10 (s, 3H), 4.26 (br, 1H), 4.86 (d, 1H, J = 16.7 Hz), 4.93 (d, 1H, J = 16.7 Hz), 5.91 (br, 1H), 6.85 (dd, 1H, J = 4.8, 7.5 Hz), 7.28 (br, 2H), 7.37 (d, 1H, J = 8.3 Hz), 7.72 (br, 1H), 7.78 (d, 1H, J = 8.6 Hz), 8.97 (br, 1H).

5 FAB-MS (m/s); 776 (M+1)⁺

Compound 70b

¹H-NMR (DMSO-d₆) δ; 2.20 (s, 3H), 2.43 (dd, 1H, J = 4.8, 14.3 Hz), 3.17 (t, 2H, J = 7.1 Hz), 3.21 (t, 2H, J = 7.1 Hz), 3.32 (dd, 1H, J = 7.4, 14.3 Hz), 4.00 (s, 3H), 4.23 (br, 1H), 4.50 (br, 4H), 4.84 (d, 1H, J = 15.9 Hz), 4.93 (d, 1H, J = 15.9 Hz), 6.00 (br, 1H), 6.87 (dd, 1H, J = 4.8, 7.4 Hz), 7.32 (dd, 1H, J = 1.7, 8.3 Hz), 7.34 (dd, 1H, J = 1.7, 8.4 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.72 (s, 1H), 7.76 (d, 1H, J = 8.4 Hz), 8.08 (s, 1H), 8.09 (s, 1H), 9.04 (br, 1H).

15 FAB-MS (m/s); 612 (M+1)⁺

Compound 70c

¹H-NMR (CDCl₃) δ; 1.95 (dd, 1H, J = 4.8, 14.0 Hz), 2.13 (s, 3H), 2.92 (t, 2H, J = 7.1 Hz), 3.16 (t, 2H, J = 7.1 Hz), 3.34 (dd, 1H, J = 7.4, 14.0 Hz), 3.70 (m, 4H), 3.92 (s, 3H), 4.67 (t, 2H, J = 5.3 Hz), 4.99 (d, 1H, J = 5.8 Hz), 6.28 (br, 1H), 7.08 (dd, 1H, J = 4.8, 7.4 Hz), 7.32 (dd, 1H, J = 1.7, 8.4 Hz), 7.34 (dd, 1H, J = 1.7, 8.4 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.82 (d, 1H, J = 8.4 Hz), 8.59 (s, 1H), 9.03 (br, 1H).

20 FAB-MS (m/s); 556 (M+1)⁺

Example 70 Synthesis of Compound 71

25 To a solution of 55 mg (0.1 mmol) of Compound 70c in 5 ml of methylene chloride were added 0.5 ml of triethylamine and 71 mg (0.4 mmol) of isonicotinoyl chloride hydrochloride, followed by stirring at room temperature for 3 hours. The reaction mixture was poured into ice-cooled 1 N hydrochloric acid, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. After

the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 32 mg (42%) of Compound 71.

¹H-NMR (CDCl₃) δ; 1.97 (dd, 1H, J = 4.9, 13.9 Hz), 2.12 (s, 3H), 3.30 (br, 5H), 3.91 (s, 3H), 4.58 (dt, 2H, J = 2.2, 6.7 Hz), 4.65 (t, 2H, J = 6.7 Hz), 4.97 (br, 2H), 6.29 (s, 1H), 7.09 (dd, 1H, J = 4.9, 7.1 Hz), 7.45 (d, 2H, J = 8.6 Hz), 7.85 (br, 5H), 8.66 (s, 1H), 8.77 (d, 4H, J = 6.1 Hz), 8.81 (d, 4H, J = 6.1 Hz), 9.01 (d, 1H, J = 1.5 Hz).

FAB-MS (m/s); 766 (M+1)⁺

10 **Example 71 Synthesis of Compounds 72a and 72b**

The same procedure as in Example 23 was repeated using 110 mg (0.2 mmol) of Compound c and 0.32 ml (2.0 mmol) of methyloxalyl chloride give a product. The same procedure as in Example 68 was repeated using the obtained product to give 12.2 mg (11%) of Compound 72a and 37.2 mg (31%) of Compound 72b.

15

Compound 72a

¹H-NMR (CDCl₃) δ; 2.16 (s, 3H), 2.72 (dd, 1H, J = 4.8, 14.4 Hz), 3.43 (dd, 1H, J = 7.6, 14.4 Hz), 3.77 (s, 3H), 3.78 (s, 2H), 4.09 (s, 3H), 4.64 (d, 1H, J = 16.3 Hz), 4.75 (d, 1H, J = 16.3 Hz), 4.85 (br, 1H), 5.54 (br, 1H), 6.80 (dd, 1H, J = 4.8, 7.6 Hz), 7.36 (d, 1H, J = 7.3 Hz), 7.39 (dt, 1H, J = 0.8, 7.3 Hz), 7.50 (s, 2H), 7.88 (d, 1H, J = 7.3 Hz), 7.91 (d, 1H, J = 8.3 Hz), 8.82 (br, 1H).

FAB-MS (m/s); 540 (M+1)⁺

Compound 72b

25 ¹H-NMR (CDCl₃) δ; 2.00 (dd, 1H, J = 4.7, 14.0 Hz), 2.15 (s, 3H), 3.30 (s, 1H), 3.65 (s, 6H), 3.84 (s, 2H), 3.90 (s, 2H), 3.93 (s, 3H), 5.00 (d, 2H, J = 5.4 Hz), 6.33 (s, 1H), 7.12 (dd, 1H, J = 4.7, 7.1 Hz), 7.36 (d, 1H, J = 7.3 Hz), 7.85 (d, 1H, J = 7.3 Hz), 7.94 (d, 1H, J = 7.3 Hz), 7.95 (s, 1H), 8.05 (d, 1H, J = 7.3 Hz), 8.62 (br, 1H), 9.08 (s, 1H).

FAB-MS (m/s); 612 (M+1)⁺

Example 72 Synthesis of Compounds 73a, 73b and 73c

The same procedure as in Examples 68 and 69 was repeated using 141 mg (0.2 mmol) of
5 Compound 27 to give 56 mg (67%) of Compound 73a, 3.0 mg (2.4%) of Compound 73b and 27 mg
(23%) of Compound 73c.

Compound 73a

FAB-MS (m/s); 804 (M+1)⁺

10

Compound 73b

¹H-NMR (CDCl₃) δ ; 2.10-2.18 (m, 4H), 2.21 (s, 3H), 2.29 (dd, 1H, J = 4.9, 14.3 Hz),
2.92 (t, 2H, J = 7.4 Hz), 2.94 (t, 2H, J = 7.4 Hz), 3.27 (dd, 1H, J = 7.5, 14.3 Hz),
4.24 (s, 3H), 4.26 (t, 2H, J = 7.4 Hz), 4.28 (t, 2H, J = 7.4 Hz), 5.02 (d, 2H, J = 6.4
15 Hz), 6.09 (br, 1H), 6.88 (dd, 1H, J = 2.7, 4.7 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.37
(d, 1H, J = 8.3 Hz), 7.42 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 1.7 Hz), 7.72 (d, J =
8.3 Hz), 8.12 (s, 1H), 8.14 (s, 1H), 9.14 (d, 1H, J = 1.2 Hz).

FAB-MS (m/s); 640 (M+1)⁺

20

Compound 73c

¹H-NMR (CDCl₃) δ; 1.85 (s, 4H), 1.97 (dd, 1H, J = 4.9, 14.1 Hz), 2.17 (s, 3H), 2.81 (dt,
4H, J = 10.0, 16.0 Hz), 3.33 (dd, 1H, J = 7.1, 14.1 Hz), 3.50 (t, 4H, J = 6.4 Hz),
3.92 (s, 3H), 4.49 (br, 2H), 4.99 (d, 1H, J = 5.4 Hz), 6.27 (s, 1H), 7.07 (dd, 1H, J =
4.9, 7.3 Hz), 7.32 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.82 (s, 1H), 7.83
25 (d, 1H, J = 8.4 Hz), 9.03 (d, 1H, J = 1.2 Hz).

FAB-MS (m/s); 584 (M+1)⁺

Example 73 Synthesis of Compound 74

To a solution of 31 mg (0.05 mmol) of Compound 22 in 3 ml of N,N-dimethylformamide was added 15 mg of 10% Pd/C, followed by stirring in a hydrogen atmosphere at 60 °C for 5 hours. After insoluble materials were removed by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give 12 mg (20%) of Compound 74.

¹H-NMR (CDCl₃) δ; 2.05 (br, 4H), 2.20 (s, 3H), 2.44 (dd, 1H, J = 4.9, 14.4 Hz), 2.88 (t, 2H, J = 7.4 Hz), 2.92 (t, 2H, J = 7.4 Hz), 3.32 (dd, 1H, J = 7.4, 14.4 Hz), 3.47 (t, 2H, J = 7.4 Hz), 3.48 (t, 2H, J = 7.4 Hz), 3.78 (s, 6H), 4.00 (s, 3H), 4.12(br, 1H), 4.85 (d, 1H, J = 15.8 Hz), 4.92 (d, 1H, J = 15.8 Hz), 5.93 (br, 1H), 6.85 (dd, 1H, J = 4.9, 7.4 Hz), 7.30 (br, 2H), 7.34 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 1.3 Hz), 7.74 (d, 1H, J = 7.3 Hz), 8.98 (d, 1H, J = 1.0 Hz).

FAB-MS (m/s); 612 (M+1)⁺

15

Example 74 Synthesis of Compound 75

To a solution of 50 mg (0.06 mmol) of Compound 70a in 3 ml of N,N-dimethylformamide was added 0.5 ml of piperidine, followed by stirring at room temperature overnight. Water was added to the reaction mixture, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give 10 mg (15%) of Compound 75.

20

¹H-NMR (CDCl₃) δ; 1.55 (br, 10H)§ 2.19 (s, 3H), 2.31 (dd, 1H, J = 4.9, 7.6 Hz), 2.53 (br, 8H), 2.66 (br, 2H), 2.74 (br, 2H), 3.02 (br, 2H), 3.26 (dd, 1H, J = 6.8, 7.5 Hz), 4.09 (s, 3H), 4.93 (d, 2H, J = 10.2 Hz), 6.09 (br, 1H), 6.86 (dd, 1H, J = 4.9, 7.3 Hz), 7.35 (br, 3H), 7.71 (d, 1H, J = 8.6 Hz), 7.74 (d, 1H, J = 1.5 Hz), 9.08 (br, 1H).

FAB-MS (m/s); 690 (M+1)⁺

Example 75 **Synthesis of Compound 76**

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 70a and 0.5 ml of morpholine to give 24 mg (59%) of Compound 76.

5 ¹H-NMR (CDCl₃) δ; 2.20 (s, 3H), 2.29 (dd, 1H, J = 4.9, 14.4 Hz), 2.69 (br, 8H), 2.71 (br, 4H), 3.01 (br, 4H), 3.26 (dd, 1H, J = 7.4, 14.4 Hz), 3.78 (br, 8H), 3.89 (br, 1H), 4.09 (s, 3H), 4.98 (d, 2H, J = 4.9 Hz), 6.11 (s, 1H), 6.87 (dd, 1H, J = 4.9, 7.4 Hz), 7.34 (br, 2H), 7.70 (d, 1H, J = 8.5 Hz), 7.71 (d, 1H, J = 8.5 Hz), 7.74 (d, 1H, J = 1.2 Hz), 9.12 (s, 1H).

10 FAB-MS (m/s); 694 (M+1)⁺

Example 76 **Synthesis of Compound 77**

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 70a and 0.5 ml of diethylamine to give 7.3 mg (18%) of Compound 77.

15 ¹H-NMR (CDCl₃) δ; 1.12 (t, 6H, J = 7.2 Hz), 1.14 (t, 6H, J = 7.2 Hz), 2.19 (s, 3H), 2.37 (dd, 1H, J = 4.9, 14.4 Hz), 2.68 (q, 4H, J = 7.2 Hz), 2.72 (q, 4H, J = 7.2 Hz), 2.83 (br, 4H), 2.95 (br, 4H), 3.29 (dd, 1H, J = 7.4, 14.4 Hz), 4.09 (s, 3H), 4.88 (d, 1H, J = 16.4 Hz), 4.96 (d, 1H, J = 16.4 Hz), 6.05 (br, 1H), 6.86 (dd, 1H, J = 4.9, 7.4 Hz), 7.29 (br, 2H), 7.36 (d, 1H, J = 8.3 Hz), 7.70 (s, 1H), 7.73 (d, 1H, J = 8.3 Hz), 9.03 (s, 1H).

20 FAB-MS (m/s); 666 (M+1)⁺

Example 77 **Synthesis of Compound 78**

25 The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 70a and 1 ml of N-methylethanolamine to give 8.3 mg (21%) of Compound 78.

1¹H-NMR (CDCl₃) δ; 1.60 (br, 2H), 2.18 (s, 3H), 2.31 (dd, 1H, J = 4.9, 14.4 Hz), 2.40 (s, 3H), 2.41 (s, 3H), 2.64 (t, 2H, J = 5.1 Hz), 2.66 (t, 2H, J = 5.1 Hz), 3.01 (br, 4H),

3.26 (br, 5H), 3.59 (t, 2H, J = 5.1, 14.4 Hz), 3.61 (t, 2H, J = 5.1, 14.4 Hz), 4.08 (s, 3H), 4.89 (d, 1H, J = 16.4 Hz), 4.98 (d, 1H, J = 16.4 Hz), 6.19 (br, 1H), 6.85 (dd, 1H, J = 4.9, 7.3 Hz), 7.28 (d, 1H, J = 8.3 Hz), 7.31 (d, 1H, J = 8.3 Hz), 7.38 (d, 1H, J = 8.3 Hz), 7.69 (br, 1H), 7.72 (d, 1H, J = 8.3 Hz), 9.09 (s, 1H).

5 FAB-MS (m/s); 670 ($M+1$)⁺

Example 78 **Synthesis of Compound 79**

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 70a and 0.5 ml of a 1.0 N solution of methylamine in ethanol to give 12 mg (34%) of 10 Compound 79.

¹H-NMR ($CDCl_3$) δ ; 2.15 (s, 3H), 2.23 (br, 1H), 2.47 (s, 3H), 2.49 (s, 3H), 2.94 (br, 2H), 3.00 (br, 6H), 3.25 (dd, 1H, J = 7.3, 14.4 Hz), 4.08 (s, 3H), 4.88 (d, 1H, J = 16.6 Hz), 4.95 (d, 1H, J = 16.6 Hz), 6.21 (br, 1H), 6.85 (dd, 1H, J = 4.9, 7.1 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.31 (d, 1H, J = 8.3 Hz), 7.39 (d, 1H, J = 8.3 Hz), 7.69 (s, 1H), 7.71 (d, 1H, J = 8.3 Hz), 9.08 (s, 1H).

15 FAB-MS (m/s); 582 ($M+1$)⁺

Example 79 **Synthesis of Compound 80**

20 To a solution of 78 mg (0.1 mmol) of Compound 70a in 3 ml of methylene chloride was added 0.78 ml (6.0 mmol) of p-methoxybenzylamine, followed by reflux for 1 day. Water was added to the reaction mixture, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel 25 column chromatography (chloroform/methanol = 10/1) to give 47 mg (59%) of Compound 80.

¹H-NMR ($CDCl_3$) δ ; 2.16 (s, 3H), 2.33 (dd, 1H, J = 4.9, 7.3 Hz), 3.02 (br, 8H), 3.25 (dd, 1H, J = 7.3, 14.4 Hz), 3.764 (s, 3H), 3.769 (s, 3H), 3.773 (s, 4H), 4.08 (s, 3H),

4.79 (d, 1H, $J = 16.7$ Hz), 4.87 (d, 1H, $J = 16.7$ Hz), 6.10 (br, 1H), 6.63- 7.03 (br, 5H), 7.10-7.34 (br, 7H), 7.67 (s, 1H), 7.71 (d, 1H, $J = 8.5$ Hz), 9.05 (s, 1H).

FAB-MS (m/s); 794 (M+1)⁺

5 **Example 80 Synthesis of Compound 81**

To a solution of 20 mg (0.026 mmol) of Compound 70a in 3 ml of dimethylsulfoxide was added 9.8 mg (0.15 mmol) of sodium azide, followed by stirring at room temperature overnight. Water was added to the reaction mixture, and precipitates were removed by filtration. After the filtrate was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 14 mg (89%) of Compound 81.

10 ¹H-NMR (DMSO-d₆) δ ; 1.97 (dd, 1H, $J = 4.9, 13.9$ Hz), 2.13 (s, 3H), 3.05 (t, 2H, $J = 7.0$ Hz), 3.09 (t, 2H, $J = 7.0$ Hz), 3.36 (dd, 1H, $J = 7.3, 13.9$ Hz), 3.66 (t, 2H, $J = 7.0$ Hz), 3.69 (t, 2H, $J = 7.0$ Hz), 3.92 (s, 3H), 5.00 (br, 2H), 6.30 (s, 1H), 7.10 (dd, 1H, $J = 4.9, 7.3$ Hz), 7.39 (dd, 1H, $J = 1.7, 8.3$ Hz), 7.41 (dd, 1H, $J = 1.7, 8.3$ Hz), 15 7.84 (d, 1H, $J = 8.3$ Hz), 7.86 (d, 1H, $J = 8.3$ Hz), 7.95 (dd, 1H, $J = 1.5$ Hz), 8.62 (br, 1H), 9.09 (dd, 1H, $J = 1.5$ Hz).

FAB-MS (m/s); 606 (M+1)⁺

20 **Example 81 Synthesis of Compound 82**

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 73a and 2.0 ml of piperidine to give 16 mg (36%) of Compound 82.

25 ¹H-NMR (CDCl₃) δ ; 1.43 (br, 4H), 1.60 (br, 12H), 1.90 (br, 4H), 2.20 (s, 3H), 2.31 (dd, 1H, $J = 4.9, 14.4$ Hz), 2.38-2.50 (br, 8H), 2.78-2.86 (br, 4H), 3.27 (dd, 1H, $J = 7.3, 14.4$ Hz), 4.09 (s, 3H), 4.97 (d, 2H, $J = 6.4$ Hz), 6.07 (br, 1H), 6.86 (dd, 1H, $J = 4.9, 7.3$ Hz), 7.30 (m, 2H), 7.38 (d, 1H, $J = 8.3$ Hz), 7.700 (d, 1H, $J = 8.3$ Hz), 7.703 (d, 1H, $J = 1.5$ Hz), 9.07 (br, 1H).

FAB-MS (m/s); 718 (M+1)⁺

Example 82 Synthesis of Compound 83

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 73a and 0.3 ml of morpholine to give 11 mg (26%) of Compound 83.

5

HNMR (DMSO-d₆) δ; 1.81 (br, 4H), 1.97 (dd, 1H, J = 4.6, 14.9 Hz), 2.19 (br, 12H), 2.21 (s, 3H), 2.83 (br, 4H), 3.59 (br, 9H), 3.92 (s, 3H), 4.98 (d, 2H, J = 4.6 Hz), 6.28 (br, 1H), 7.07 (dd, 1H, J = 4.6, 7.3 Hz), 7.32 (d, 1H, J = 2.0, 8.8 Hz), 7.33 (d, 1H, J = 2.0, 8.8 Hz), 7.77 (d, 1H, J = 8.8 Hz), 7.81 (d, 1H, J = 8.8 Hz), 7.83 (d, 1H, J = 1.0 Hz), 8.57 (s, 1H), 9.04 (d, 1H, J = 1.0 Hz).

10

FAB-MS (m/s); 722 (M+1)⁺

Example 83 Synthesis of Compound 84

The same procedure as in Example 74 was repeated using 50 mg (0.06 mmol) of Compound 73a and 0.5 ml of diethylamine to give 7.9 mg (19%) of Compound 84.

20

¹H-NMR (DMSO-d₆) δ; 0.97 (t, 6H, J = 7.1 Hz), 0.98 (t, 6H, J = 7.1 Hz), 1.81 (br, 12H), 1.97 (dd, 1H, J = 4.9, 14.5 Hz), 2.12 (s, 3H), 2.28 (t, 2H, J = 8.8 Hz), 2.30 (t, 2H, J = 8.8 Hz), 2.41-2.49 (br, 4H), 3.30 (br, 1H), 3.92 (s, 3H), 4.99 (d, 2H, J = 5.4 Hz), 6.28 (s, 1H), 7.07 (dd, 1H, J = 4.9, 7.3 Hz), 7.32 (dd, 1H, J = 1.9, 8.5 Hz), 7.33 (dd, 1H, J = 1.9, 8.5 Hz), 7.77 (d, 1H, J = 8.5 Hz), 7.81 (s, 1H), 7.83 (d, 1H, J = 8.5 Hz), 8.56 (s, 1H), 9.04 (d, 1H, J = 1.5 Hz).

FAB-MS (m/s); 694 (M+1)⁺

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Example 84 Synthesis of Compound 85

Step A

To a solution of 1.0 g (1.25 mmol) of Compound 73a in 10 ml of dimethylsulfoxide was added 488 mg (7.5 mmol) of sodium azide, followed by stirring at room temperature overnight. Water was added to the reaction mixture, and precipitates were collected by filtration. To a solution of 310 mg (about 0.43 mmol) of the obtained product in 5.0 ml of chloroform/methanol (9/1) was

30

added 2.6 g (10 mmol) of triphenylphosphine, followed by stirring at room temperature overnight. To the reaction mixture was added water, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 497 mg (quantitative) of a diamino compound.

5 **Step B**

To a solution of 58 mg (0.1 mmol) of the diamino compound in 2.0 ml of methylene chloride was added 0.075 ml (0.5 mmol) of ethyl isocyanate, followed by stirring at room temperature overnight. To the reaction mixture was added water, followed by extraction with 10 chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give 2.0 mg (2.7%) of Compound 85.

15 $^1\text{H-NMR}$ (DMSO-d₆) δ : 0.99 (t, 3H, J = 7.2 Hz), 1.00 (t, 3H, J = 7.2 Hz), 1.78 (br, 4H), 1.97 (dd, 1H, J = 4.8, 14.1 Hz), 2.12 (s, 3H), 2.76 (br, 4H), 3.10 (br, 8H), 3.37 (br, 1H), 3.92 (s, 3H), 5.00 (br, 2H), 5.74 (br, 2H), 5.86 (br, 2H), 6.28 (br, 1H), 7.07 (dd, 1H, J = 4.8, 7.3 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 8.4 Hz), 7.82 (s, 1H), 7.83 (d, 1H, J = 8.4 Hz), 8.58 (s, 1H), 9.03 (d, 1H, J = 1.5 Hz).

20 FAB-MS (m/s); 724 (M+1)⁺

Example 85 **Synthesis of Compound 86**

To a solution of 58 mg (0.1 mmol) of the diamino compound obtained in Example 84, Step A in 2.0 ml of methylene chloride were added 0.5 ml of pyridine and 91 mg (0.5 mmol) of di-t-butyl 25 dicarbonate, followed by stirring at room temperature overnight. To the reaction mixture was added water, followed by extraction with chloroform/methanol(9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 10/1) to give 8.0 mg (10%) of Compound 86.

¹H-NMR (CDCl₃) δ; 1.45 (s, 18H), 1.92 (br, 4H), 2.19 (s, 3H), 2.40 (dd, 1H, J = 4.6, 14.4 Hz), 2.80 (br, 4H), 3.23 (br, 4H), 3.31 (dd, 1H, J = 7.3, 14.4 Hz), 4.09 (s, 3H), 4.67 (br, 2H), 4.79 (d, 1H, J = 16.4 Hz), 4.89 (d, 1H, J = 16.4 Hz), 5.98 (br, 1H), 6.85 (dd, 1H, J = 4.6, 7.3 Hz), 7.25-7.29 (m, 2H), 7.35 (d, 1H, J = 8.3 Hz), 7.65 (br, 1H), 7.73 (d, 1H, J = 8.3 Hz), 8.95 (s, 1H).

5 FAB-MS (m/s); 782 (M+1)⁺

Example 86 Synthesis of Compound 87

The same procedure as in Example 68 was repeated using 45 mg (0.070 mmol) of
10 Compound 43 to give 20 mg (46%) of Compound 87.

¹H-NMR (CDCl₃) δ; 1.97 (dd, 1H, J = 4.9, 13.8 Hz), 2.14 (s, 6H), 2.16 (s, 3H), 2.79-2.89 (br, 4H), 2.97-3.09 (br, 4H), 3.35 (dd, 1H, J = 7.3, 13.8 Hz), 3.92 (s, 3H), 5.00 (br, 2H), 6.29 (s, 1H), 7.09 (dd, 1H, J = 4.9, 7.3 Hz), 7.36 (dd, 1H, J = 1.7, 8.5 Hz), 15 7.38 (dd, 1H, J = 1.7, 8.5 Hz), 7.80 (d, 1H, J = 8.5 Hz), 7.83 (d, 1H, J = 8.5 Hz), 7.90 (d, 1H, J = 1.5 Hz), 8.59 (br, 1H), 9.05 (d, 1H, J = 1.2 Hz).

FAB-MS (m/s); 616 (M+1)⁺

Example 87 Synthesis of Compound 88

20 The same procedure as in Example 68 was repeated using 886 mg (1.3 mmol) of Compound 44 to give 710 mg (85%) of Compound 88.

¹H-NMR (CDCl₃) δ; 1.31 (t, 3H, J = 7.3 Hz), 1.33 (t, 3H, J = 7.3 Hz), 2.18 (s, 3H), 2.60-2.68 (m, 5H), 2.86 (br, 2H), 2.94 (br, 2H), 3.06 (br, 2H), 3.12 (br, 2H), 3.37 (dd, 1H, J = 7.3, 14.1 Hz), 4.09 (s, 3H), 4.75 (d, 1H, J = 16.1 Hz), 4.83 (d, 1H, J = 16.1 Hz), 5.73 (s, 1H), 6.82 (dd, 1H, J = 4.9, 7.3 Hz), 7.24 (dd, 1H, J = 1.7, 8.3 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.33 (dd, 1H, J = 1.7, 8.5 Hz), 7.71 (d, 1H, J = 1.2 Hz), 15 7.80 (d, 1H, J = 8.5 Hz), 8.85 (br, 1H).

FAB-MS (m/s); 644 (M+1)⁺

Example 88 **Synthesis of Compound 89**

To a solution of 77 mg (0.1 mmol) of Compound 70a in 2 ml of N,N-dimethylformamide were added 0.025 ml (0.24 mmol) of methyl 2-mercaptoproacetate and 138 mg (1.0 mmol) of 5 potassium carbonate, followed by stirring at room temperature for 2 hours. To the reaction mixture was added water, followed by extraction with chloroform/methanol(9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 37 mg (51%) of Compound 89.

10

¹H-NMR (CDCl₃) δ; 1.96 (dd, 1H, J = 5.3, 14.0 Hz), 2.13 (s, 3H), 3.00 (br, 8H), 3.30 (br, 1H), 3.43 (s, 2H), 3.46 (s, 2H), 3.67 (s, 3H), 3.68 (s, 3H), 3.91 (s, 3H), 5.01 (br, 2H), 6.31 (br, 1H), 7.09 (dd, 1H, J = 5.3, 7.7 Hz), 7.35 (dd, 1H, J = 1.6, 8.7 Hz), 7.37 (dd, 1H, J = 1.6, 8.7 Hz), 7.81 (d, 1H, J = 8.7 Hz), 7.84 (d, 1H, J = 8.7 Hz), 15 7.89 (s, 1H), 8.62 (s, 1H), 9.04 (s, 1H).

FAB-MS (m/s); 732 (M+1)⁺

Example 89 **Synthesis of Compound 90**

The same procedure as in Example 88 was repeated using 77 mg (0.1 mmol) of Compound 20 70a and 0.027 ml (0.24 mmol) of ethyl 3-mercaptopropionate to give 43 mg (55%) of Compound 90.

25

¹H-NMR (CDCl₃) δ; 1.23 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz), 2.18 (br, 3H), 2.59-3.62 (br, 5H), 2.83-2.89 (m, 6H), 2.96 (br, 2H), 3.02-3.07 (br, 2H), 3.10-3.16 (m, 2H), 3.37 (dd, 1H, J = 7.6, 14.4 Hz), 4.08 (s, 3H), 4.15 (m, 4H), 4.73 (d, 1H, J = 16.6 Hz), 4.75 (br, 1H), 4.83 (d, 1H, J = 16.6 Hz), 5.76 (br, 1H), 6.83 (dt, 1H, J = 4.9, 7.6 Hz), 7.23 (dd, 1H, J = 8.7 Hz), 7.27 (d, 1H, J = 8.8 Hz), 7.32 (dd, 1H, J = 1.7, 8.8 Hz), 7.70 (s, 1H), 7.80 (d, 1H, J = 8.8 Hz), 8.83 (s, 1H).

FAB-MS (m/s); 788 (M+1)⁺

Example 90 Synthesis of Compound 91

The same procedure as in Example 68 was repeated using 65 mg (0.081 mmol) of Compound 50 to give 42 mg (67%) of Compound 91.

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¹H-NMR (DMSO-d₆) δ; 1.97 (dd, 1H, J = 4.7, 7.9 Hz), 2.08 (s, 3H), 3.00-3.05 (br, 4H), 3.15-3.21 (br, 4H), 3.39 (br, 1H), 3.91 (s, 3H), 5.00 (br, 2H), 6.30 (s, 1H), 6.79 (dt, 4H, J = 2.2, 8.8 Hz), 7.32 (br, 10H), 7.79 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.6 Hz), 7.86 (s, 1H), 9.04 (d, 1H, J = 1.2 Hz), 9.54 (s, 1H), 9.55 (s, 1H).

10 FAB-MS (m/s); 772 (M+1)⁺

Example 91 Synthesis of Compound 92

The same procedure as in Example 68 was repeated using 38 mg (0.05 mmol) of Compound 51 to give 22 mg (56%) of Compound 92.

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¹H-NMR (DMSO-d₆) δ; 1.97 (dd, 1H, J = 4.9, 13.8 Hz), 2.06 (s, 8H), 2.13 (s, 3H), 3.21-3.25 (m, 4H), 3.36 (dd, 1H, J = 7.3, 13.8 Hz), 3.92 (s, 3H), 3.94 (t, 2H, J = 7.3 Hz), 3.97 (t, 2H, J = 7.3 Hz), 5.01 (br, 2H), 6.30 (br, 1H), 7.10 (dd, 1H, J = 4.9, 7.3 Hz), 7.40 (d, 1H, J = 1.7, 8.3 Hz), 7.42 (dd, 1H, J = 1.7, 8.3 Hz), 7.84 (d, 1H, J = 7.3 Hz), 7.86 (d, 1H, J = 8.3 Hz), 7.98 (d, 1H, J = 1.4 Hz), 8.63 (br, 1H), 9.08 (d, 1H, J = 1.2 Hz).

20 FAB-MS (m/s); 756 (M+1)⁺

Example 92 Synthesis of Compound 93

25 The same procedure as in Example 46 was repeated using 31 mg (0.05 mmol) of Compound 69 to give 10 mg (26%) of Compound 93.

¹H-NMR (CDCl₃) δ; 2.28 (s, 3H), 2.30 (dd, 1H, J = 4.9, 14.2 Hz), 3.17-3.21 (br, 2H), 3.33 (t, 2H, J = 7.3 Hz), 3.42-3.46 (m, 3H), 3.48-3.52 (m, 2H), 3.63 (t, 2H, J =

7.2 Hz), 4.09 (s, 3H), 4.99 (br, 1H), 6.27 (br, 1H), 6.88 (dd, 1H, J = 4.9, 7.0 Hz), 7.09 (d, 2H, J = 6.4 Hz), 7.12 (d, 2H, J = 6.4 Hz), 7.31 (dd, 1H, J = 1.5, 8.3 Hz), 7.33 (dd, 1H, J = 1.7, 8.3 Hz), 7.43 (d, 1H, J = 8.3 Hz), 7.68 (s, 1H), 7.76 (d, 1H, J = 8.4 Hz), 8.21 (d, 2H, J = 6.4 Hz), 8.34 (d, 2H, J = 6.4 Hz), 9.19 (s, 1H).

5 FAB-MS (m/s); 742 (M+1)⁺

Example 93 Synthesis of Compound 94

The same procedure as in Example 47 was repeated using 77 mg (0.1 mmol) of Compound 70a to give 21 mg (28%) of Compound 94.

10 ¹H-NMR (CDCl₃) δ ; 2.16 (s, 3H), 2.78 (dd, 1H, J = 4.7, 14.4 Hz), 3.14 (br, 2H), 3.27 (t, 2H, J = 7.2 Hz), 3.41 (dd, 1H, J = 7.4, 14.4 Hz), 3.50 (br, 2H), 3.63 (t, 2H, J = 7.2 Hz), 4.03 (s, 3H), 4.69 (br, 1H), 5.08 (br, 1H), 5.45 (br, 3H), 6.79 (dd, 1H, J = 4.7, 7.4 Hz), 6.99 (br, 2H), 7.25 (br, 4H), 7.40 (dd, 1H, J = 1.7, 8.5 Hz), 7.48 (br, 2H), 7.75 (s, 1H), 7.85 (d, 1H, J = 8.5 Hz), 8.52 (br, 2H), 8.78 (s, 1H).

15 FAB-MS (m/s); 742 (M+1)⁺

Example 94 Synthesis of Compound 95

20 The same procedure as in Example 68 was repeated using 60 mg (0.089 mmol) of Compound 53 to give 20 mg (35%) of Compound 95.

25 ¹H-NMR (DMSO-d₆) δ ; 1.95 (m, 5H), 2.08 (s, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 2.55 (t, 4H, J = 7.6 Hz), 2.86 (t, 2H, J = 7.6 Hz), 2.88 (t, 2H, J = 7.6 Hz), 3.34 (dd, 1H, J = 7.3, 14.1 Hz), 3.92 (s, 3H), 4.99 (d, 2H, J = 4.9 Hz), 6.28 (s, 1H), 7.08 (dd, 1H, J = 4.9, 7.3 Hz), 7.32 (dd, 1H, J = 2.7, 8.5 Hz), 7.38 (dd, 1H, J = 1.7, 8.5 Hz), 7.79 (d, 1H, J = 8.5 Hz), 7.83 (d, 1H, J = 1.2 Hz), 7.84 (d, 1H, J = 8.5 Hz), 8.57 (br, 1H), 9.04 (s, 1H).

FAB-MS (m/s); 644 (M+1)⁺

Example 95 **Synthesis of Compound 96**

The same procedure as in Example 88 was repeated using 80 mg (0.1 mmol) of Compound 73a and 34 mg (0.20 mmol) of 2-mercaptopbenzothiazole to give 35 mg (40%) of Compound 96.

5 $^1\text{H-NMR}$ (DMSO-d₆) δ ; 1.97 (dd, 1H, J = 4.9, 14.0 Hz), 2.12 (s, 3H), 2.18-2.22 (m, 4H),
2.96-3.00 (m, 4H), 3.33 (br, 3H), 3.44 (t, 2H, J = 2.8 Hz), 3.91 (s, 3H), 4.97 (br, 2H), 6.29 (s, 1H), 7.08 (dd, 1H, J = 4.9, 7.3 Hz), 7.26-7.52 (m, 6H), 7.80-8.00 (m, 7H), 8.56 (br, 1H), 9.07 (d, 1H, J = 1.2 Hz).

10 FAB-MS (m/s); 882 (M+1)⁺

Example 96 **Synthesis of Compound 97**

To a solution of 335 mg (1.5 mmol) of palladium (II) acetate in 5 ml of N,N-dimethylformamide was added 1.82 mg (6.0 mmol) of bis(o-tolyl)phosphine, followed by stirring in an argon stream at room temperature for 30 minutes. To the mixture were added a solution of 3.29 15 g (5.0 mmol) of Compound B in 30 ml of N,N-dimethylformamide, 0.60 ml (80 mmol) of triethylamine and 0.28 ml (2.1 mmol) of 2-vinylpyridine, followed by stirring at 60 °C for 3 hours. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give 2.24 g (66%) of Compound 97.

20 $^1\text{H-NMR}$ (DMSO-d₆) δ ; 1.79 (s, 3H), 2.13 (dd, 1H, J = 5.1, 15.4 Hz), 2.32 (s, 3H), 2.77 (s, 3H), 3.99 (dd, 1H, J = 7.3, 15.4 Hz), 4.02 (s, 3H), 5.35 (br, 2H), 6.98 (dd, 1H, J = 5.1, 7.3 Hz), 7.15 (ddd, 1H, J = 1.0, 4.8, 7.8 Hz), 7.47 (d, 1H, J = 8.8 Hz), 7.48 (d, 1H, J = 7.8 Hz), 7.69 (dt, 1H, J = 1.7, 8.8 Hz), 7.78 (dd, 1H, J = 1.7, 8.8 Hz), 7.83 (d, 1H, J = 16.1 Hz), 8.01 (br, 2H), 8.08 (dd, 1H, J = 1.7, 7.8 Hz), 8.46 (d, 1H, J = 1.5 Hz), 8.63 (ddd, 1H, J = 0.7, 1.7, 4.9 Hz), 9.29 (d, 1H, J = 1.5 Hz), 10.20 (s, 1H).

25 FAB-MS (m/s); 683 (M+1)⁺

Example 97 **Synthesis of Compound 98**

The same procedure as in Example 57 was repeated using 1.0 g (1.4 mmol) of Compound 97 to give 870 mg (87%) of Compound 98.

FAB-MS (m/s); 685 (M+1)⁺

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Example 98 **Synthesis of Compound 99**

The same procedure as in Example 1, Step B was repeated using 174 mg (0.25 mmol) of Compound 98 to give 150 mg (98%) of Compound 99.

10 ¹H-NMR (DMSO-d₆) δ; 2.04 (dd, 1H, J = 4.9,13.9 Hz), 2.15 (s, 3H), 3.42 (dd, 1H, J = 7.3, 13.9 Hz), 4.72 (s, 2H), 5.02 (d, 1H, J = 5.4 Hz), 6.34 (s, 1H), 7.17 (dd, 1H, J = 4.9, 7.3 Hz), 7.26-7.29 (m, 2H), 7.30 (d, 1H, J = 16.1 Hz), 7.46 (dd, 1H, J = 1.5, 8.1 Hz), 7.65 (d, 1H, J = 8.1 Hz), 7.85-7.89 (m, 6H), 8.61 (dd, 1H, J = 1.0, 3.9 Hz), 9.46 (d, 1H, J = 1.2 Hz).FAB-MS (m/s); 685 (M+1)⁺

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Example 99 **Synthesis of Compound 100**

To a solution of 100 mg (0.15 mmol) of Compound 98 in 5 ml of methylene chloride were added 54 mg (0.36 mmol) of t-butyldimethylsilyl chloride, 75 mg (0.75 mmol) of imidazole and 0.5 ml of triethylamine, followed by stirring for 1 hour. The reaction mixture was poured into ice-cold 20 water, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was triturated with hexane to give 110 mg (92%) of Compound 100.

FAB-MS (m/z); 799 (M+1)⁺

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Example 100 **Synthesis of Compound 101**

The same procedure as in Example 1, Step B was repeated using 40 mg (0.25 mmol) of Compound 100 to give 27 mg (68%) of Compound 101.

¹H-NMR (CDCl₃) δ; 0.21 (s, 6H), 1.03 (s, 9H), 2.15 (s, 3H), 2.84 (dd, 1H, J = 4.9, 14.4 Hz), 3.50 (dd, 1H, J = 7.5, 14.4 Hz), 4.03 (s, 3H), 4.46 (d, 1H, J = 16.4 Hz), 4.63 (d, 1H, J = 16.4 Hz), 4.94 (s, 2H), 5.52 (br, 1H), 6.73 (dd, 1H, J = 4.9, 7.5 Hz), 7.14 (br, 2H), 7.16 (d, 1H, J = 8.5 Hz), 7.42 (d, 1H, J = 7.5 Hz), 7.44 (dd, 1H, J = 1.5, 8.5 Hz), 7.50 (dd, 1H, J = 1.5, 8.5 Hz), 7.66 (dt, 1H, J = 1.7, 7.5 Hz), 7.71 (d, 1H, J = 16.1 Hz), 7.74 (s, 1H), 7.88 (d, 1H, J = 8.5 Hz), 8.61 (d, 1H, J = 3.9 Hz), 8.95 (s, 1H).

FAB-MS (m/z); 715 (M+1)⁺

10 **Example 101** **Synthesis of Compound 102**

To a solution of 90 mg (0.15 mmol) of Compound 99 in 3.0 ml of chloroform/methanol (5/1) was added 104 mg (0.45 mmol) of camphor sulfonic acid, followed by stirring at room temperature for 1 day. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate, followed by extraction with chloroform/methanol (9/1). The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 64 mg (52%) of Compound 102.

¹H-NMR (DMSO-d₆) δ; 2.04 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 3.37 (s, 3H), 3.41 (dd, 1H, J = 7.5, 14.1 Hz), 3.93 (s, 3H), 4.63 (s, 2H), 5.01 (d, 1H, J = 17.2 Hz), 5.06 (d, 1H, J = 17.2 Hz), 6.38 (s, 1H), 7.17 (dd, 1H, J = 4.9, 7.3 Hz), 7.24 (m, 1H), 7.29 (d, 1H, J = 16.0 Hz), 7.46 (dd, 1H, J = 1.7, 8.7 Hz), 7.61 (d, 1H, J = 7.6 Hz), 7.79 (dt, 1H, J = 1.7, 7.6 Hz), 7.87 (dd, 1H, J = 1.7, 8.7 Hz), 7.88 (d, 1H, J = 16.0 Hz), 7.92 (d, 1H, J = 8.7 Hz), 7.99 (d, 1H, J = 1.0 Hz), 8.59 (d, 1H, J = 3.8 Hz), 8.69 (s, 1H), 9.45 (d, 1H, J = 1.4 Hz).

FAB-MS (m/s); 615 (M+1)⁺

Example 102 **Synthesis of Compound 103**

The same procedure as in Example 101 was repeated using a solution of 60 mg (0.10 mmol) of Compound 99 in 3.0 ml of methylene chloride/ethanol (2/1) and 255 mg (1.1 mol) of camphorsulfonic acid to give 23 mg (41%) of Compound 103.

5 ¹H-NMR (CDCl₃) δ; 1.33 (t, 3H, J = 6.9 Hz), 2.18 (s, 3H), 2.62 (dd, 1H, J = 4.9, 14.5 Hz), 3.44 (dd, 1H, J = 7.4, 14.5 Hz), 3.66 (q, 2H, J = 6.9 Hz), 4.08 (s, 3H), 4.67 (d, 1H, J = 15.9 Hz), 4.71 (s, 2H), 4.82 (d, 1H, J = 15.9 Hz), 5.77 (s, 1H), 6.82 (dd, 1H, J = 4.9, 7.4 Hz), 7.14 (ddd, 1H, J = 1.0, 4.9, 7.6 Hz), 7.21 (d, 1H, J = 16.1 Hz), 7.32 (d, 1H, J = 8.8 Hz), 7.46 (d, 1H, J = 8.8 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.64 (dd, 1H, J = 1.7, 7.6 Hz), 7.68 (dt, 1H, J = 1.7, 7.6 Hz), 7.80 (d, 1H, J = 16.1 Hz), 7.83 (d, 1H, J = 1.2 Hz), 7.83 (d, 1H, J = 8.3 Hz), 8.63 (dd, 1H, J = 0.7, 3.9 Hz), 9.21 (d, 1H, J = 1.2 Hz).

10 FAB-MS (m/s); 629 (M+1)⁺

15 **Example 103 Synthesis of Compound 104**

To a solution of 137 mg (0.20 mmol) of Compound 98 in 3.0 ml of methylene chloride was added 0.13 ml (2.0 mmol) of N,N-dimethylethanolamine and 510 mg (2.2 mol) of camphorsulfonic acid, followed by reflux for 1 day. The reaction was poured into a saturated aqueous solution of sodium hydrogen carbonate, followed by extraction with chloroform/methanol (9/1). The extract 20 was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give diacetylated Compound 104. The same procedure as in Example 1, Step B was repeated using the obtained diacetylated compound to give 21 mg (16%) of Compound 104.

25 ¹H-NMR (DMSO-d₆) δ; 2.03 (dd, 1H, J = 4.9, 14.2 Hz), 2.15 (s, 3H), 2.21 (m, 8H), 3.42 (m, 1H), 3.60 (t, 2H, J = 5.9 Hz), 3.93 (s, 3H), 4.69 (s, 2H), 4.99 (d, 1H, J = 17.1 Hz), 5.05 (d, 1H, J = 17.1 Hz), 6.37 (s, 1H), 7.17 (dd, 1H, J = 4.9, 7.3 Hz), 7.24 (m, 1H), 7.30 (d, 1H, J = 16.0 Hz), 7.46 (dd, 1H, J = 1.5, 8.7 Hz), 7.61 (d, 1H, J = 7.9 Hz), 7.67-7.97 (m, 5H), 8.00 (s, 1H), 8.58 (m, 1H), 8.69 (s, 1H), 9.45 (d, 1H, J = 1.6 Hz).

FAB-MS (m/s); 672 (M+1)⁺

Example 104 **Synthesis of Compound 105**

To a solution of 60 mg (0.10 mmol) of Compound 99 in 2 ml of methylene chloride was
5 added 0.042 ml (0.3 mmol) of trifluoroacetic anhydride, followed by stirring for 20 minutes. To the
mixture was added 0.022 ml (0.3 mmol) of ethanethiol, followed by stirring overnight. The reaction
mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate, followed by
extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of
sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced
10 pressure, the residue was purified by silica gel column chromatography (chloroform/methanol =
20/1) to give 26 mg (25%) of Compound 105.

¹H-NMR (CDCl₃) δ; 1.33 (t, 3H, J = 7.3 Hz), 2.18 (s, 3H), 2.56 (q, 2H, J = 7.3 Hz), 2.68
(dd, 1H, J = 4.9, 14.4 Hz), 3.46 (dd, 1H, J = 7.3, 14.4 Hz), 3.85 (s, 2H), 4.08 (s,
15 3H), 4.65 (d, 1H, J = 16.4 Hz), 4.69 (d, 1H, J = 16.4 Hz), 5.75 (s, 2H), 6.81 (dd,
1H, J = 4.9, 7.3 Hz), 7.18 (m, 1H), 7.19 (d, 1H, J = 15.9 Hz), 7.28 (dd, 1H, J =
1.7, 8.8 Hz), 7.43 (dd, 1H, J = 1.7, 8.8 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.60 (d, 1H,
J = 8.8 Hz), 7.68 (dt, 1H, J = 1.5, 7.6 Hz), 7.79 (br, 3H), 8.62 (dd, 1H, J = 0.4,
3.7 Hz), 9.13 (s, 1H).

20 FAB-MS (m/s); 645 (M+1)⁺

Example 105 **Synthesis of Compound 106**

The same procedure as in Example 103 was repeated using a solution of 137 mg (0.20
mmol) of Compound 98 in 3.0 ml of methylene chloride, 113 mg (0.8 mmol) of N,N-
25 dimethylethanethiol hydrochloride and 510 mg (2.2 mmol) of camphorsulfonic acid to give 6.1 mg
(4.3%) of Compound 106.

¹H-NMR (DMSO-d₆) δ; 2.03 (dd, 1H, J = 4.9, 14.2 Hz), 2.14 (s, 3H), 2.19 (s, 6H), 2.52
(br, 4H), 3.40 (br, 1H), 3.93 (s, 3H), 3.99 (s, 2H), 4.99 (d, 1H, J = 17.1 Hz), 5.03

(d, 1H, J = 17.1 Hz), 6.37 (s, 1H), 7.17 (dd, 1H, J = 4.9, 7.4 Hz), 7.23 (m, 1H),
7.30 (d, 1H, J = 15.9 Hz), 7.47 (dd, 1H, J = 1.7, 8.9 Hz), 7.60 (d, 1H, J = 7.6 Hz),
7.79 (dd, 1H, J = 1.8, 8.9 Hz), 7.87 (dd, 1H, J = 1.7, 8.9 Hz), 7.88 (d, 1H, J =
15.9 Hz), 7.90 (d, 1H, J = 8.7 Hz), 7.95 (d, 1H, J = 8.7 Hz), 7.97 (d, 1H, J = 1.5
Hz), 8.58 (m, 1H), 8.70 (s, 1H), 9.45 (d, 1H, J = 1.5 Hz).

5 FAB-MS (m/s); 688 (M+1)⁺

Example 106 Synthesis of Compound 107

The same procedure as in Example 103 was repeated using a solution of 137 mg (0.20
10 mmol) of Compound 98 in 3.0 ml of methylene chloride, 111 mg (1.0 mmol) of 2-mercaptopypyridine
and 510 mg (2.2 mmol) of camphorsulfonic acid to give 33 mg (24%) of Compound 107.

15 ¹H-NMR (DMSO-d₆) δ; 2.00 (dd, 1H, J = 4.9, 14.5 Hz), 2.13 (s, 3H), 3.40 (br, 1H), 3.92
(s, 3H), 4.66 (s, 2H), 4.95 (d, 1H, J = 17.6 Hz), 4.99 (d, 1H, J = 17.6 Hz), 6.32 (s,
1H), 7.16 (dd, 2H, J = 4.9, 7.6 Hz), 7.24 (br, 1H), 7.29 (d, 1H), 7.36 (d, 1H, J =
7.6 Hz), 7.54 (dd, 1H, J = 1.7, 8.7 Hz), 7.60 (d, 1H, J = 7.6 Hz), 7.67 (dt, 1H, J =
1.7, 7.6 Hz), 7.79 (dt, 1H, J = 1.7, 7.6 Hz), 7.88 (br, 3H), 7.94 (d, 1H, J = 8.8
Hz), 8.10 (d, 1H, J = 1.5 Hz), 8.53 (br, 1H), 8.58 (br, 1H), 8.67 (s, 1H), 9.44 (d,
1H, J = 1.2 Hz).

20 FAB-MS (m/s); 694 (M+1)⁺

Example 107 Synthesis of Compound 108

The same procedure as in Example 103 was repeated using a solution of 68 mg (0.10
mmol) of Compound 98 in 3.0 ml of methylene chloride, 150 mg (1.0 mmol) of 2-
25 mercaptobenzimidazole and 510 mg (2.2 mmol) of camphorsulfonic acid to give 22 mg (30%) of
Compound 108.

30 ¹H-NMR (DMSO-d₆) δ; 1.99 (dd, 1H, J = 4.9, 14.1 Hz), 2.12 (s, 3H), 3.38 (dd, 1H, J =
4.9, 6.9 Hz), 3.92 (s, 3H), 4.79 (d, 2H, J = 3.4 Hz), 4.84 (d, 1H, J = 16.4 Hz),
4.93 (d, 1H, J = 16.4 Hz), 6.30 (s, 1H), 7.18 (br, 5H), 7.24 (d, 1H, J = 15.9 Hz),

7.28 (dd, 1H, J = 15.9 Hz), 7.38 (dd, J = 1.9, 7.6 Hz), 7.60 (br, 2H), 7.79 (dt, 1H, J = 1.9, 7.6 Hz), 7.87 (br, 2H), 7.94 (d, 1H, J = 8.6 Hz), 8.15 (s, 1H), 8.59 (d, 1H, J = 1.8 Hz), 9.21 (s, 1H), 9.43 (s, 1H), 12.2 (s, 1H).

FAB-MS (m/s); 733 ($M+1$)⁺

5

Example 108 Synthesis of Compound 109

To a suspension of 68 mg (0.10 mmol) of Compound 97 in 3.0 ml of methylene chloride were added 0.016 ml (0.22 mmol) of ethanethiol, and 0.018 ml (0.15 mol) of boron trifluoride etherate, followed by stirring at room temperature for 1 hour. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 21 mg (27%) of Compound 109.

FAB-MS (m/s); 789 ($M+1$)⁺

Example 109 Synthesis of Compound 110

The same procedure as in Example 1, Step B was repeated using 21 mg (0.25 mmol) of Compound 109 to give 15 mg (88%) of Compound 110.

¹H-NMR (DMSO-d₆) δ ; 1.22 (dt, 6H, J = 2.5, 7.3 Hz), 2.03 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 2.58 (br, 4H), 3.41 (dd, 1H, J = 7.3, 14.1 Hz), 3.93 (s, 3H), 4.98 (d, 1H, J = 17.1 Hz), 5.04 (d, 1H, J = 17.1 Hz), 5.43 (s, 1H), 6.35 (s, 1H), 7.18 (dd, 1H, J = 4.9, 7.3 Hz), 7.25 (br, 1H), 7.30 (d, 1H, J = 16.1 Hz), 7.61 (br, 2H), 7.80 (dt, 1H, J = 1.7, 7.6 Hz), 7.88 (d, 1H, J = 16.1 Hz), 7.89 (d, 1H, J = 16.1 Hz), 7.93 (d, 1H, J = 8.8 Hz), 7.96 (d, 1H, J = 8.8 Hz), 8.09 (d, 1H, J = 1.4 Hz), 8.59 (dd, 1H, J = 0.8, 3.2 Hz), 8.71 (s, 1H), 9.45 (d, 1H, J = 0.6 Hz).

30 FAB-MS (m/s); 705 ($M+1$)⁺

Example 110 Synthesis of Compound 111

The same procedure as in Example 96 was repeated using 1.5 g (2.1 mmol) of Compound J to give 893 mg (62%) of Compound 111.

5

$^1\text{H-NMR}$ (CDCl_3) δ ; 1.81 (s, 3H), 2.16 (dd, 1H, J = 5.1, 14.6 Hz), 2.34 (s, 3H), 2.75 (s, 3H), 4.01 (dd, 1H, J = 7.3, 14.6 Hz), 4.03 (s, 3H), 5.31 (d, 2H, J = 2.0 Hz), 6.99 (dd, 1H, J = 5.1, 7.3 Hz), 7.18 (ddd, 1H, J = 1.0, 4.9, 7.6 Hz), 7.30 (d, 1H, J = 16.1 Hz), 7.52 (d, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 8.8 Hz), 7.72 (dt, 1H, J = 1.7, 7.6 Hz), 7.82 (dd, 1H, J = 1.7, 8.8 Hz), 7.85 (d, 1H), 7.93 (d, 1H, J = 8.8 Hz), 8.03 (dd, 1H, J = 1.5, 8.8 Hz), 8.09 (d, 1H, J = 1.3 Hz), 8.66 (dd, 1H, J = 1.0, 4.6 Hz), 9.57 (d, 1H, J = 1.6 Hz), 10.16 (s, 1H).

FAB-MS (m/z); 683 (M+1)⁺

15 **Example 111 Synthesis of Compound 112**

The same procedure as in Example 57 was repeated using 750 mg (1.1 mmol) of Compound 111 to give 620 mg (82%) of Compound 112.

FAB-MS (m/z); 685 (M+1)⁺

20

Example 112 Synthesis of Compound 113

The same procedure as in Example 1, Step B was repeated using 620 mg (0.91 mmol) of Compound 112 to give 450 mg (83%) of Compound 113.

25

$^1\text{H-NMR}$ (CDCl_3) δ ; 1.99 (dd, 1H, J = 5.0, 13.7 Hz), 2.16 (s, 3H), 3.17 (s, 1H), 3.30 (m, 1H), 3.93 (s, 3H), 4.67 (s, 2H), 5.09 (d, 2H, J = 3.5 Hz), 7.13 (dd, 1H, J = 5.0, 7.3 Hz), 7.25 (dd, 1H, J = 5.0, 7.6 Hz), 7.41 (d, 1H, J = 16.1 Hz), 7.48 (dd, 1H, J = 1.5, 8.7 Hz), 7.60 (d, 1H, J = 7.6 Hz), 7.80 (dt, 1H, J = 1.6, 7.6 Hz), 7.84 (dd, 1H, J = 1.2, 8.7 Hz), 7.85 (d, 1H, J = 8.7 Hz), 7.94 (d, 1H, J = 8.7 Hz), 7.95 (d, 1H, J

= 16.1 Hz), 8.29 (d, 1H, J = 0.9 Hz), 8.59 (d, 1H, J = 4.0 Hz), 8.69 (s, 1H), 9.16 (s, 1H).

FAB-MS (m/z); 601 (M+1)⁺

5

Example 113 **Synthesis of Compound 114**

The same procedure as in Example 99 was repeated using 82 mg (0.12 mmol) of Compound 112 to give 110 mg (72%) of Compound 114.

10 FAB-MS (m/z); 798 (M+1)⁺

Example 114 **Synthesis of Compound 115**

The same procedure as in Example 1, Step B was repeated using 30 mg (0.038 mmol) of Compound 114 to give 12 mg (44%) of Compound 115.

15

¹H-NMR (CDCl₃) δ; 0.13 (s, 3H), 0.15 (s, 3H), 0.97 (s, 9H), 2.19 (s, 3H), 2.73 (dd, 1H, J = 4.6, 14.4 Hz), 3.48 (dd, 1H, J = 7.3, 14.4 Hz), 4.09 (s, 3H), 4.45 (d, 1H, J = 16.5 Hz), 4.68 (d, 1H, J = 16.5 Hz), 4.74 (d, 1H, J = 12.2 Hz), 4.80 (d, 1H, J = 12.2 Hz), 5.69 (br, 1H), 6.81 (dd, 1H, J = 4.6, 7.3 Hz), 7.08 (d, 1H, J = 16.1 Hz), 7.19 (ddd, 1H, J = 0.7, 4.9, 7.3 Hz), 7.29 (d, 1H, J = 8.5 Hz), 7.38 (d, 1H, J = 7.8 Hz), 7.40 (dd, 1H, J = 1.4, 8.5 Hz), 7.62 (br, 2H), 7.71 (d, 1H, J = 16.1 Hz), 7.80 (s, 1H), 7.84 (d, 1H, J = 8.5 Hz), 8.60 (d, 1H, J = 3.9 Hz), 8.75 (s, 1H).

FAB-MS (m/z); 715 (M+1)⁺

25 **Example 115** **Synthesis of Compound 116**

The same procedure as in Example 1, Step B was repeated using 60 mg (0.10 mmol) of Compound 113 to give 37 mg (40%) of Compound 116.

30 ¹H-NMR (CDCl₃) δ; 2.20 (s, 3H), 2.65 (d, 1H, J = 15.0 Hz), 3.33 (s, 3H), 3.49 (dd, 1H, J = 7.4, 15.0 Hz), 4.08 (s, 3H), 4.32-4.66 (m, 4H), 5.86 (s, 1H), 6.85 (dd, 1H, J =

4.6, 7.3 Hz), 6.99 (d, 1H, J = 16.1 Hz), 7.10 (dd, 1H, J = 4.9, 7.4 Hz), 7.36 (br, 2H), 7.39 (dd, 1H, J = 0.5, 8.8 Hz), 7.60 (br, 4H), 7.72 (s, 1H), 7.80 (d, 1H, J = 8.8 Hz), 8.57 (d, 1H, J = 3.9 Hz), 8.72 (s, 1H).

FAB-MS (m/s); 615 (M+1)⁺

5

Example 116 **Synthesis of Compound 117**

The same procedure as in Example 102 was repeated using 60 mg (0.10 mmol) of Compound 113 to give 32 mg (51%) of Compound 117.

10 ¹H-NMR (CDCl₃) δ; 1.26 (t, 3H, J = 7.2 Hz), 2.21 (s, 3H), 2.63 (dd, 1H, J = 4.6, 14.4 z), 3.34 (dd, 1H, J = 7.4, 14.4 Hz), 3.55 (q, 2H, J = 7.2 Hz), 4.10 (s, 3H), 4.50 (d, 1H, J = 11.5 Hz), 4.57 (d, 1H, J = 16.6 Hz), 4.58 (d, 1H, J = 11.5 Hz), 4.77 (d, 1H, J = 16.6 Hz), 5.81 (s, 1H), 6.86 (dd, 1H, J = 4.6, 7.5 Hz), 7.15 (br, 2H), 7.36 (d, 1H, J = 8.6 Hz), 7.40 (d, 1H, J = 7.8 Hz), 7.45 (dd, 1H, J = 1.7, 8.6 Hz), 7.64 (br, 3H), 7.74 (d, 1H, J = 16.1 Hz), 7.84 (d, 1H, J = 8.5 Hz), 7.87 (s, 1H), 8.61 (d, 1H, J = 3.6 Hz), 8.86 (s, 1H).

FAB-MS (m/s); 629 (M+1)⁺

Example 117 **Synthesis of Compound 118**

20 The same procedure as in Example 104 was repeated using 60 mg (0.10 mmol) of Compound 113 to give 30 mg (46%) of Compound 118.

15 ¹H-NMR (CDCl₃) δ; 1.24 (t, 3H, J = 7.3 Hz), 2.22 (s, 3H), 2.45 (q, 2H, J = 7.3 Hz), 2.62 (dd, 1H, J = 4.6, 14.5 z), 3.50 (dd, 1H, J = 7.3, 14.5 Hz), 3.71 (d, 1H, J = 14.9 Hz), 3.77 (d, 1H, J = 14.9 Hz), 4.10 (s, 3H), 4.46 (d, 1H, J = 16.6 Hz), 4.71 (d, 1H, J = 16.6 Hz), 5.80 (s, 1H), 6.87 (dd, 1H, J = 4.6, 7.3 Hz), 7.04 (d, 1H, J = 16.7 Hz), 7.12 (ddd, 1H, J = 0.7, 5.2, 7.6 Hz), 7.37 (br, 2H), 7.43 (dd, 1H, J = 1.7, 8.6 Hz), 7.62 (br, 3H), 7.78 (s, 1H), 7.81 (d, 1H, J = 8.6 Hz), 8.59 (d, 1H, J = 3.9 Hz), 8.75 (s, 1H).

FAB-MS (m/s); 645 (M+1)⁺

Example 118 **Synthesis of Compound 119**

The same procedure as in Example 106 was repeated using 60 mg (0.10 mmol) of
5 Compound 113 to give 28 mg (40%) of Compound 119.

10 ¹H-NMR (CDCl₃) δ; 2.00 (dd, 1H, J = 4.9, 13.9 Hz), 2.16 (s, 3H), 3.32 (br, 1H), 3.93 (s,
1H), 4.62 (s, 2H), 5.10 (s, 2H), 6.40 (s, 1H), 7.12 (br, 2H), 7.26 (br, 1H), 7.34 (d,
1H, J = 7.9 Hz), 7.41 (d, 1H, J = 16.1 Hz), 7.54 (dd, 1H, J = 2.0, 8.6 Hz), 7.65
(br, 2H), 7.81 (br, 3H), 7.94 (s, 1H), 7.97 (d, 1H, J = 6.9 Hz), 8.29 (s, 1H), 8.60
(s, 1H), 8.65 (d, 1H, J = 7.1 Hz), 8.70 (s, 1H), 9.28 (s, 1H).

FAB-MS (m/s); 694 (M+1)⁺

Example 119 **Synthesis of Compound 120**

15 To a solution of 90 mg (0.15 mmol) of Compound 113 in 3.0 ml of methylene chloride was
added 225 mg (1.0 mmol) of 2-mercaptopbenzimidazole and 695 mg (3.0 mmol) of camphorsulfonic
acid, followed by reflux for 1 day. The reaction mixture was poured into a saturated aqueous
solution of sodium hydrogencarbonate, followed by extraction with chloroform/methanol (9/1). The
extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium
20 sulfate. The solvent was evaporated under reduced pressure to give 26 mg (24%) of Compound
120.

25 ¹H-NMR (DMSO-d₆) δ; 2.00 (dd, 1H, J = 4.8, 13.9 Hz), 2.16 (s, 3H), 3.92 (m, 1H), 3.93
(s, 3H), 4.79 (s, 2H), 5.10 (s, 2H), 6.40 (s, 1H), 7.13 (br, 5H), 7.26 (dd, 1H, J =
5.4, 6.9 Hz), 7.41 (d, 1H, J = 16.1 Hz), 7.59 (br, 3H), 7.84 (br, 3H), 7.94 (d, 1H, J
= 8.9 Hz), 7.95 (d, 1H, J = 16.1 Hz), 8.29 (s, 1H), 8.59 (d, 1H, J = 4.0 Hz), 8.71
(s, 1H), 9.30 (d, 1H, J = 1.4 Hz), 12.6 (br, 1H).

FAB-MS (m/s); 733 (M+1)⁺

Example 120 Synthesis of Compound 121

The same procedure as in Example 96 was repeated using 146 mg (0.20 mmol) of Compound 67 to give 57 mg (mixture of E and Z, 40%) of Compound 121.

5 FAB-MS (m/s); 709 (M+1)⁺

Example 121 Synthesis of Compound 122

The same procedure as in Example 1, Step B was repeated using 57 mg (0.080 mmol) of Compound 121 to give 32 mg (64%) of Compound 122.

10 FAB-MS (m/s); 625 (M+1)⁺

Example 122 Synthesis of Compound 123

The same procedure as in Example 62 was repeated using 68 mg (0.1 mmol) of Compound 100 to give 34 mg (50%) of Compound 123.

FAB-MS (m/z); 802 (M+1)⁺

Example 123 Synthesis of Compound 124

20 The same procedure as in Example 1, Step B was repeated using 40 mg (0.050 mmol) of Compound 123 to give 11 mg (31%) of Compound 124.

¹H-NMR (CDCl₃) δ; 0.19 (s, 6H), 1.02 (s, 9H), 2.19 (s, 3H), 2.51 (dd, 1H, J = 4.9, 14.4 Hz), 3.23 (br, 4H), 3.34 (dd, 1H, J = 7.3, 14.4 Hz), 4.08 (s, 3H), 4.38 (br, 1H), 4.80 (d, 1H, J = 16.4 Hz), 4.88 (d, 1H, J = 16.4 Hz), 4.96 (s, 2H), 5.89 (br, 1H), 6.83 (dd, 1H, J = 4.9, 7.3 Hz), 7.11 (ddd, 1H, J = 1.0, 4.9, 7.3 Hz), 7.16 (d, 1H, J = 7.6 Hz), 7.28 (br, 2H), 7.42 (dd, 1H, J = 1.7, 8.8 Hz), 7.56 (dt, 1H, J = 2.0, 7.6 Hz), 7.80 (d, 1H, J = 8.8 Hz), 7.87 (d, 1H, J = 1.0 Hz), 8.58 (ddd, 1H, J = 0.73, 1.7, 3.9 Hz), 9.02 (s, 1H).

FAB-MS (m/z); 716 (M+1)⁺

Example 124 **Synthesis of Compounds 125a and 125b**

To a solution of 80 mg (0.1 mmol) of Compound 123 in 6 ml of chloroform/methanol (5/1) 5 was added 104 mg (0.45 mmol) of camphorsulfonic acid, followed by stirring at 40 °C for 1 day. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was 10 evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 12 mg (17%) of Compound 125a and 38 mg (58%) of Compound 125b.

Compound 125a

FAB-MS (m/s); 701 (M+1)⁺

15

Compound 125b

FAB-MS (m/z); 659 (M+1)⁺

Example 125 **Synthesis of Compound 126**

20 The same procedure as in Example 1, Step B was repeated using 38 mg (0.057 mmol) of Compound 125b to give 21 mg (60%) of Compound 126.

¹H-NMR (CDCl₃) δ; 2.14 (s, 3H), 2.49 (dd, 1H, J = 4.9, 14.4 Hz), 3.19 (br, 4H), 3.34 (dd, 1H, J = 7.3, 14.4 Hz), 3.50 (s, 3H), 4.07 (s, 3H), 4.64 (d, 1H, J = 16.7 Hz), 4.65 (s, 2H), 4.75 (d, 1H, J = 16.6 Hz), 6.04 (br, 1H), 6.82 (dd, 1H, J = 4.6, 7.3 Hz), 7.10 (dd, 1H, J = 4.6, 7.3 Hz), 7.14 (d, 1H, J = 7.6 Hz), 7.22 (dd, 1H, J = 1.7, 8.5 Hz), 7.28 (d, 1H, J = 8.5 Hz), 7.42 (dd, 1H, J = 1.5, 8.8 Hz), 7.56 (dt, 1H, J = 1.7, 7.6 Hz), 7.79 (s, 1H), 7.82 (d, 1H, J = 8.8 Hz), 8.57 (d, 1H, J = 4.8 Hz), 8.93 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z); 617 (M+1)⁺

Example 126 **Synthesis of Compounds 127a and 127b**

The same procedure as in Example 102 was repeated using 80 mg (0.1 mmol) of
5 Compound 123 to give diacetylated Compounds 127a and 127b. The same procedure as in
Example 1, Step B was repeated using diacetylated Compounds 127a and 127b to give 14.6 mg
(23%) of Compound 127a and 11.0 mg (18%) of Compound 127b.

Compound 127a

10 ¹H-NMR (CDCl₃) δ; 1.33 (t, 3H, J = 7.1 Hz), 2.12 (s, 3H), 2.58 (dd, 1H, J = 4.8, 14.4
Hz), 3.17 (br, 4H), 3.37 (dd, 1H, J = 7.3, 14.4 Hz), 3.65 (q, 2H, J = 7.1 Hz), 4.05
(s, 3H), 4.58 (d, 1H, J = 16.6 Hz), 4.67 (d, 1H, J = 16.6 Hz), 4.69 (s, 2H), 5.95 (s,
1H), 6.80 (dd, 1H, J = 4.8, 7.3 Hz), 7.11 (ddd, 1H, J = 1.0, 4.9, 7.6 Hz), 7.15 (d,
1H, J = 7.6 Hz), 7.17 (dd, 1H, J = 1.8, 8.6 Hz), 7.23 (d, 1H, J = 8.5 Hz), 7.43 (dd,
15 1H, J = 1.5, 8.5 Hz), 7.56 (dt, 1H, J = 1.8, 7.6 Hz), 7.78 (s, 1H), 7.83 (d, 1H, J =
8.5 Hz), 8.57 (br, 1H), 8.83 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z); 631 (M+1)⁺

Compound 127b

20 ¹H-NMR (CDCl₃) δ; 1.98 (dd, 1H, J = 4.9, 14.4 Hz), 2.14 (s, 3H), 3.29 (br, 4H), 3.36
(dd, 1H, J = 7.3, 14.4 Hz), 3.92 (s, 3H), 4.71 (d, 2H, J = 5.7 Hz), 4.98 (d, 2H, J =
4.9 Hz), 5.21 (t, 1H, J = 5.7 Hz), 6.30 (s, 1H), 7.08 (dd, 1H, J = 4.9, 7.3 Hz), 7.21
(ddd, 1H, J = 1.0, 4.9, 7.3 Hz), 7.32 (d, 1H, J = 7.6 Hz), 7.35 (dd, 1H, J = 1.7, 8.6
Hz), 7.44 (dd, 1H, J = 1.4, 8.6 Hz), 7.69 (dt, 1H, J = 1.7, 7.6 Hz), 7.78 (d, 1H, J =
8.6 Hz), 7.88 (d, 1H, J = 8.6 Hz), 7.96 (s, 1H), 8.53 (ddd, 1H, J = 0.7, 1.7, 4.5
Hz), 8.59 (s, 1H), 9.10 (d, 1H, J = 1.4 Hz).

FAB-MS (m/z); 603 (M+1)⁺

Example 127 **Synthesis of Compound 128**

The same procedure as in Example 106 was repeated using 80 mg (0.1 mmol) of Compound 123 to give 42 mg (54%) of Compound 128.

FAB-MS (m/z); 780 (M+1)⁺

5

Example 128 Synthesis of Compound 129

The same procedure as in Example 1, Step B was repeated using 42 mg (0.057 mmol) of Compound 128 to give 13 mg (33%) of Compound 129.

10 $^1\text{H-NMR}$ (CDCl_3) δ ; 2.14 (s, 3H), 2.66 (dd, 1H, J = 4.9, 14.4. Hz), 3.18 (br, 4H), 3.39 (dd, 1H, J = 7.6, 14.4 Hz), 4.06 (s, 3H), 4.58 (s, 2H), 4.63 (d, 1H, J = 13.4 Hz), 4.70 (d, 1H, J = 13.4 Hz), 5.71 (br, 1H), 6.77 (dd, 1H, J = 4.9, 7.6 Hz), 7.02 (ddd, 1H, J = 1.1, 1.2, 7.3 Hz), 7.12 (ddd, 1H, J = 1.2, 4.9, 7.6. Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.22 (d, 2H, J = 7.3 Hz), 7.55 (br, 4H), 7.81 (d, 1H, J = 8.8 Hz), 7.92 (d, 1H, J = 1.5 Hz), 8.52 (ddd, 1H, J = 1.0, 1.7, 4.9 Hz), 8.59 (ddd, 1H, J = 1.0, 1.9, 4.9 Hz), 8.78 (s, 1H).

15

FAB-MS (m/z); 679 (M+1)⁺

Example 129 **Synthesis of Compound 130**

The same procedure as in Example 62 was repeated using 600 mg (0.057 mmol) of Compound 114 to give 423 mg (71%) of Compound 130.

5

FAB-MS (m/z); 801 (M+1)⁺

Example 130 **Synthesis of Compound 131**

The same procedure as in Example 1, Step B was repeated using 30 mg (0.037 mmol) of 10 Compound 130 to give 9.0 mg (34%) of Compound 131.

15

¹H-NMR (CDCl₃) δ; 0.17 (s, 3H), 0.18 (s, 3H), 1.00 (s, 9H), 2.15 (s, 3H), 2.70 (dd, 1H, J = 4.9, 14.3 Hz), 3.26-3.36 (m, 4H), 3.39 (dd, 1H, J = 7.3, 14.3 Hz), 4.08 (s, 3H), 4.67 (d, 1H, J = 16.4 Hz), 4.73 (d, 1H, J = 16.4 Hz), 4.92 (s, 2H), 5.70 (br, 2H), 5.70 (br, 1H), 6.79 (dd, 1H, J = 4.9, 7.3 Hz), 7.16 (ddd, 1H, J = 1.2, 4.9, 7.1 Hz), 7.20 (dt, 1H, J = 1.0, 7.6 Hz), 7.28 (br, 2H), 7.41 (dd, 1H, J = 1.7, 8.5 Hz), 7.62 (dt, 1H, J = 1.9, 7.6 Hz), 7.68 (d, 1H, J = 1.5 Hz), 7.78 (d, 1H, J = 8.5 Hz), 8.60 (ddd, 1H, J = 1.0, 2.0, 4.8 Hz), 8.90 (s, 1H).

FAB-MS (m/z); 717 (M+1)⁺

20

Example 131 **Synthesis of Compounds 132**

The same procedure as in Example 101 was repeated using 80 mg (0.1 mmol) of Compound 130 to give diacetylated Compound 132. The same procedure as in Example 1, Step B was repeated using diacetylated Compound 132 to give 36.5 mg (59%) of Compound 132.

25

¹H-NMR (CDCl₃) δ; 2.12 (s, 3H), 2.86 (dd, 1H, J = 4.9, 14.4 Hz), 3.28-3.45 (m, 4H), 3.43 (s, 3H), 3.47 (dd, 1H, J = 7.3, 14.4 Hz), 4.06 (s, 3H), 4.43-4.59 (m, 4H), 5.70 (br, 1H), 5.75 (br, 1H), 6.73 (dd, 1H, J = 4.9, 7.3 Hz), 7.15 (ddd, 1H, J = 1.2, 4.9, 7.3 Hz), 7.17 (d, 1H, J = 8.5 Hz), 7.20 (d, 1H, J = 7.6 Hz), 7.21 (dd, 1H, J =

1.7, 8.5 Hz), 7.60 (d, 1H, J = 1.7 Hz), 7.61 (dt, 1H, J = 1.7, 7.6 Hz), 7.82 (d, 1H, J = 8.5 Hz), 8.56 (ddd, 1H, J = 1.0, 1.7, 4.9 Hz), 8.72 (d, 1H, J = 1.2 Hz).

FAB-MS (m/z); 617 (M+1)⁺

5 **Example 132 Synthesis of Compounds 133**

The same procedure as in Example 102 was repeated using 80 mg (0.1 mmol) of Compound 130 to give diacetylated Compound 133. The same procedure as in Example 1, Step B was repeated using diacetylated Compound 133 to give 4.9 mg (7.8%) of Compound 133.

10 ¹H-NMR (CDCl₃) δ; 1.31 (t, 3H, J = 7.0 Hz), 2.13 (s, 3H), 2.78 (dd, 1H, J = 5.1, 14.6 Hz), 3.48 (br, 4H), 3.71 (q, 2H, J = 7.0 Hz), 4.07 (s, 3H), 4.55-5.13 (m, 4H), 5.71 (br, 1H), 5.75 (br, 1H), 6.76 (dd, 1H, J = 5.1, 7.3 Hz), 7.15 (ddd, 1H, J = 1.0, 4.9, 7.3 Hz), 7.22 (br, 3H), 7.36 (dd, 1H, J = 1.7, 8.8 Hz), 7.61 (dd, 1H, J = 1.7, 7.8 Hz), 7.64 (d, 1H, J = 0.8 Hz), 7.80 (d, 1H, J = 8.8 Hz), 8.57 (ddd, 1H, J = 0.9, 1.9, 4.9 Hz), 8.83 (d, 1H, J = 1.0 Hz).

15 FAB-MS (m/z); 631 (M+1)⁺

Example 133 Synthesis of Compounds 134

The same procedure as in Example 104 was repeated using 80 mg (0.1 mmol) of Compound 130 to give diacetylated Compound 134. The same procedure as in Example 1, Step B was repeated using diacetylated Compound 134 to give 16 mg (23%) of Compound 134.

20 ¹H-NMR (CDCl₃) δ; 1.30 (t, 3H, J = 7.3 Hz), 2.14 (s, 3H), 2.54 (q, 2H, J = 7.3 Hz), 2.78 (dd, 1H, J = 4.9, 14.4 Hz), 3.18-3.34 (m, 4H), 3.52 (dd, 1H, J = 7.3, 14.4 Hz), 3.88 (s, 3H), 4.08 (s, 3H), 4.53 (d, 1H, J = 16.6 Hz), 4.63 (d, 1H, J = 16.6 Hz), 5.68 (s, 1H), 6.78 (dd, 1H, J = 4.9, 7.3 Hz), 7.15 (ddd, 1H, J = 1.0, 4.8, 7.8 Hz), 7.22 (br, 3H), 7.36 (dd, 1H, J = 1.7, 8.5 Hz), 7.61 (dd, 1H, J = 1.7, 7.8 Hz), 7.63 (s, 1H), 7.80 (d, 1H, J = 8.5 Hz), 8.58 (ddd, 1H, J = 0.9, 1.7, 4.9 Hz), 8.76 (d, 1H, J = 1.2 Hz).

FAB-MS (m/z); 647 (M+1)⁺

Example 134 **Synthesis of Compound 135**

The same procedure as in Example 105 was repeated using 80 mg (0.10 mmol) of
5 Compound 130 to give 16 mg (23%) of Compound 135.

10 ¹H-NMR (CDCl₃) δ; 1.99 (dd, 1H, J = 4.9, 14.1 Hz), 2.12 (s, 3H), 2.13 (s, 6H), 2.50 (br,
4H), 3.20 (br, 4H), 3.34 (dd, 1H, J = 7.1, 14.1 Hz), 3.92 (s, 3H), 3.95 (s, 2H),
4.91 (d, 1H, J = 17.5 Hz), 4.98 (d, 1H, J = 17.5 Hz), 6.29 (s, 1H), 7.09 (dd, 1H, J
= 4.9, 7.1 Hz), 7.23 (ddd, 1H, J = 0.7, 4.9, 7.5 Hz), 7.33 (br, 2H), 7.44 (dd, 1H, J
= 1.5, 8.4 Hz), 7.71 (dt, 1H, J = 1.9, 7.6 Hz), 7.82-7.85 (m, 2H), 8.55 (ddd, 1H, J
= 0.7, 1.0, 4.9 Hz), 8.60 (s, 1H), 9.13 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z); 690 (M+1)⁺

15 **Example 135** **Synthesis of Compound 136**

The same procedure as in Example 106 was repeated using 80 mg (0.1 mmol) of
Compound 130 to give 45 mg (58%) of Compound 136.

FAB-MS (m/z); 780 (M+1)⁺

20

Example 136 **Synthesis of Compound 137**

The same procedure as in Example 1, Step B was repeated using 45 mg (0.058 mmol) of
Compound 136 to give 24 mg (59%) of Compound 137.

25 ¹H-NMR (CDCl₃) δ; 2.14 (s, 3H), 3.23 (dd, 1H, J = 4.9, 14.4 Hz), 3.22-3.34 (m, 4H),
3.51 (dd, 1H, J = 7.6, 14.4 Hz), 4.04 (s, 3H), 4.55-4.68 (m, 4H), 5.59 (br, 1H),
6.77 (dd, 1H, J = 4.9, 7.6 Hz), 7.01 (ddd, 1H, J = 1.0, 4.9, 7.6 Hz), 7.16 (ddd, 1H,
J = 1.0, 2.4, 7.6 Hz), 7.23 (br, 4H), 7.34 (dd, 1H, J = 1.5, 8.6 Hz), 7.50 (ddd, 1H,
J = 1.9, 7.6, 7.9 Hz), 7.62 (dt, 1H, J = 1.8, 7.6 Hz), 7.67 (d, 1H, J = 1.2 Hz), 7.79

(d, 1H, $J = 8.6$ Hz), 8.53 (ddd, 1H, $J = 0.7, 1.7, 4.7$ Hz), 8.59 (ddd, 1H, $J = 0.7, 1.7, 4.9$ Hz), 8.93 (s, 1H).

FAB-MS (m/z); 696 (M+1)⁺

5 **Example 137 Synthesis of Compound 138**

To a solution of 290 mg (0.40 mmol) of Compound G in 3 ml of methanol/methylene chloride (1/1) was added 4.5 mg (0.12 mmol) of sodium borohydride, followed by stirring at room temperature for 1 hour. The reaction mixture was poured into ice-cold water, followed by extraction with chloroform/methanol. The extract was washed with a saturated aqueous solution of 10 sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to give 120 mg (75%) of a hydroxymethyl compound.

The same procedure as in Example 21 was repeated using 210 mg (0.29 mmol) of the obtained hydroxymethyl compound to give 60 mg (39%) of Compound 138.

15

¹H-NMR (DMSO-d₆) δ ; 1.95 (br, 2H), 2.15 (s, 3H), 3.20 (br, 2H), 3.80 (br, 3H), 4.39 (s, 4H), 5.05 (d, 1H, $J = 7.8$ Hz), 5.15 (t, 1H, $J = 6.03$ Hz), 5.46 (s, 1H), 6.98 (m, 1H), 7.53 (dd, 1H, $J = 1.7, 8.6$ Hz), 7.55 (dd, 1H, $J = 1.7, 8.8$ Hz), 7.82 (d, 1H, $J = 8.6$ Hz), 7.96 (d, 1H, $J = 8.8$ Hz), 8.13 (d, 1H, $J = 1.2$ Hz), 8.70 (br, 1H), 9.33 (d, 1H, $J = 1.5$ Hz).

20

FAB-MS (m/s); 576 (M+1)⁺

Example 138 Synthesis of Compound 139

The same procedure as in Example 9 was repeated using 48.2 mg (0.0630 mmol) of 25 Compound 1 to give 29.0 mg (60%) of Compound 139.

¹H-NMR (DMSO-d₆) δ ; 1.96 (dd, 1H, $J = 4.9, 13.9$ Hz), 2.12 (s, 3H), 2.70-2.79 (m, 4H), 3.04-3.10 (m, 4H), 3.35 (dd, 1H, $J = 7.3, 13.9$ Hz), 3.62 (s, 3H), 3.63 (s, 3H), 3.91 (s, 3H), 4.96 (d, 1H, $J = 17.6$ Hz), 5.01 (d, 1H, $J = 17.6$ Hz), 6.28 (s, 1H),

7.08 (dd, 1H, J = 4.9, 7.3 Hz), 7.33-7.37 (m, 2H), 7.80 (d, 1H, J = 8.5 Hz), 7.83 (d, 1H, J = 8.6 Hz), 7.88 (m, 1H), 8.60 (br, 1H), 9.04 (m, 1H).

FAB-MS (m/z) ; 640 (M+1)⁺

5 **Example 139 Synthesis of Compound 140**

The same procedure as in Example 9 was repeated using 41.8 mg (0.0962 mmol) of Compound 3 to give 27.0 mg (64%) of Compound 140.

10 ¹H-NMR (DMSO-d₆) δ ; 1.19 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.96 (dd, 1H, J = 4.9, 13.9 Hz), 2.12 (s, 3H), 2.68-2.77 (m, 4H), 3.03-3.09 (m, 4H), 3.35 (dd, 1H, J = 7.2, 13.9 Hz), 3.91 (s, 3H), 4.08 (q, 2H, J = 7.1 Hz), 4.09 (q, 2H, J = .1 Hz), 4.96 (d, 1H, J = 17.7 Hz), 5.01 (d, 1H, J = 17.7 Hz), 6.28 (s, 1H), 7.08 (dd, 1H, J = 4.9, 7.2 Hz), 7.33-7.37 (m, 2H), 7.79 (d, 1H, J = 8.6 Hz), 7.83 (d, 1H, J = 8.5 Hz), 7.88 (d, 1H, J = 1.5 Hz), 8.60 (br, 1H), 9.04 (d, 1H, J = 1.0 Hz).

15 FAB-MS (m/z) ; 668 (M+1)⁺

Example 140 Synthesis of Compound 141

The same procedure as in Example 5 was repeated using 3 mg (0.536 mmol) of 2-pyridylmethyltriphenylphosphonium bromide and 82.8 mg (0.126 mmol) of Compound B to give 20 62.0 mg (E/Z = 9/1, 67%) of Compound 141.

FAB-MS (m/z) ; 733 (M+1)⁺, 735 (M+1)⁺

Example 141 Synthesis of Compound 142

25 The same procedure as in Example 1, Step B was repeated using 62.0 mg (0.0846 mmol) of Compound 141 to give 36.6 mg (E/Z = 9/1, 67%) of Compound 142.

FAB-MS (m/z) ; 649 (M+1)⁺, 651 (M+1)⁺

Example 142 Synthesis of Compound 143

To a solution of 28.1 mg (0.0433 mmol) of Compound 142 in 0.5 ml of N,N-dimethylformamide was added 2.6 mg of platinum oxide, followed by stirring in a hydrogen atmosphere at room temperature for 2 days. Insoluble materials in the reaction mixture were removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 95/5) to give 10.6 mg (38%) of Compound 143.

¹H-NMR (DMSO-d₆) δ; 2.00 (dd, 1H, J = 4.9, 14.2 Hz), 2.12 (s, 3H), 3.16-3.26 (m, 4H),

3.38 (dd, 1H, J = 7.3, 14.2 Hz), 3.91 (s, 3H), 4.94 (d, 1H, J = 18.2 Hz), 5.00 (d, 1H, J = 18.2 Hz), 6.31 (s, 1H), 7.14 (dd, 1H, J = 4.9, 7.3 Hz), 7.23 (m, 1H), 7.34 (d, 1H, J = 7.8 Hz), 7.39 (m, 1H), 7.60 (m, 1H), 7.71 (m, 1H), 7.83-7.85 (m, 2H), 7.92 (d, 1H, J = 8.8 Hz), 8.55 (m, 1H), 8.72 (s, 1H), 9.38 (d, 1H, J = 2.0 Hz).

FAB-MS (m/z) ; 651 (M+1)⁺, 653 (M+1)⁺

15

Example 143 Synthesis of Compound 144

The same procedure as in Example 5 was repeated using 547 mg (18.2 mmol) of 4-pyridylmethyltriphenylphosphonium chloride and 104 mg (0.171 mmol) of Compound a to give 42.2 mg (33%) of Compound 144.

20

FAB-MS (m/z) ; 758 (M+1)⁺

Example 144 Synthesis of Compound 145

The same procedure as in Example 1, Step B was repeated using 40.0 mg (0.0528 mmol) of Compound 144 to give 16.1 mg (45%) of Compound 145.

¹H-NMR (DMSO-d₆) δ; 2.06 (dd, 1H, J = 5.0, 14.3 Hz), 2.17 (s, 3H), 3.44 (dd, 1H, J = 7.5, 14.2 Hz), 3.95 (s, 3H), 5.09 (d, 1H, J = 17.2 Hz), 5.14 (d, 1H, J = 17.2 Hz), 6.44 (s, 1H), 7.20 (dd, 1H, J = 5.0, 7.5 Hz), 7.23 (d, 1H, J = 16.3 Hz), 7.36 (d,

1H, J = 16.3 Hz), 7.62-7.65 (m, 4H), 7.75 (d, 1H, J = 16.3 Hz), 7.82 (d, 1H, J = 16.3 Hz), 7.85 (m, 1H), 7.91 (m, 1H), 7.97-8.00 (m, 2H), 8.31 (d, 1H, J = 1.4 Hz), 8.54-8.58 (m, 4H), 8.77 (s, 1H), 9.45 (d, 1H, J = 1.6 Hz).

FAB-MS (m/z) ; 674 (M+1)⁺

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Example 145 **Synthesis of Compound 146**

The same procedure as in Example 9 was repeated using 21.3 mg (0.0316 mmol) of Compound 145 to give 6.7 mg (31%) of Compound 146.

10 ¹H-NMR (DMSO-d₆) δ; 1.97 (dd, 1H, J = 4.9, 14.1 Hz), 2.12 (s, 3H), 3.02-3.16 (m, 8H), 3.35 (dd, 1H, J = 7.3, 14.1 Hz), 3.91 (s, 3H), 4.93 (d, 1H, J = 17.6 Hz), 4.97 (d, 1H, J = 17.6 Hz), 6.30 (s, 1H), 7.08 (dd, 1H, J = 4.9, 7.3 Hz), 7.33-7.38 (m, 6H), 7.79-7.84 (m, 2H), 7.85 (m, 1H), 8.45-7.48 (m, 4H), 8.61 (m, 1H), 9.08 (m, 1H).

FAB-MS (m/z) ; 678 (M+1)⁺

15

Example 146 **Synthesis of Compound 147**

To a methylene chloride (1 ml) solution of 70.0 mg (0.0824 mmol) of the coarse phosphonium salt, which was obtained by repeating the same method as in Example 64 using 51.3 mg (0.0883 mmol) of Compound e and 44.1 mg (0.128 mmol) of triphenylphosphine hydrobromide, 20 were added 11.6 mg (0.0839 mmol) of potassium carbonate and 0.9 mg (0.0034 mmol) of 18-crown-6, followed by stirring at room temperature for 5 minutes. To the mixture was added 10.2 mg (0.106 mmol) of 2-imidazolecarboxaldehyde, followed by stirring at room temperature for 4 days. After insoluble materials in the reaction mixture were removed by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography 25 (chloroform/methanol = 95/5) to give 34.2 mg (69%) of Compound 147.

FAB-MS (m/z) ; 644 (M+1)⁺

30

Example 147 **Synthesis of Compound 148**

The same procedure as in Example 1, Step B was repeated using 34.2 mg (0.0532 mmol) of Compound 147 to give 22.3 mg (E/Z = 1/3, 75%) of Compound 148.

5 FAB-MS (m/z) ; 560(M+1)⁺

Example 148 **Synthesis of Compound 149**

The same procedure as in Example 9 was repeated using 10.1 mg (0.0181 mmol) of Compound 148 to give 6.9 mg (69%) of Compound 149.

10 ¹H-NMR (DMSO-d₆) δ; 1.99 (dd, 1H, J = 4.9, 14.1 Hz), 2.15 (s, 3H), 3.04-3.07 (m, 2H),
15 3.15-3.19 (m, 2H), 3.37 (dd, 1H, J = 7.4, 14.1 Hz), 3.92 (s, 3H), 4.98 (d, 1H, J = 17.2 Hz), 5.03 (d, 1H, J = 17.2 Hz), 6.33 (s, 1H), 7.02 (br, 2H), 7.10 (dd, 1H, J = 4.9, 7.4 Hz), 7.32 (m, 1H), 7.36 (m, 1H), 7.48 (m, 1H), 7.81 (m, 1H), 7.94 (m, 1H), 8.05 (m, 1H), 8.61 (s, 1H), 9.09 (d, 1H, J = 1.0 Hz).

15 FAB-MS (m/z) ; 562 (M+1)⁺

Example 149 **Synthesis of Compound 150**

To a solution of 75.4 mg (0.124 mmol) of Compound a in 3 ml of chloroform were added 20 0.15 ml (1.31 mmol) of dimethyl malonate and 0.015 ml of piperidine, followed by stirring under reflux for 12 hours. After cooling, the reaction mixture was poured into 4N hydrochloric acid, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by trituration with methanol to give 88.9 mg (86%) of 25 Compound 150.

¹H-NMR (CDCl₃) δ; 1.80 (s, 3H), 2.14 (dd, 1H, J = 5.1, 14.6 Hz), 2.28 (s, 3H), 2.81 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.99 (dd, 1H, J = 7.5, 14.6 Hz), 4.01 (s, 3H), 4.03 (s, 3H), 4.09 (s, 3H), 5.36 (s, 2H), 7.00 (dd, 1H, J = 5.1, 7.5 Hz), 7.53 (d, 1H, J =

9.3 Hz), 7.61-7.65 (m, 2H), 7.92 (d, 1H, J = 8.8 Hz), 7.98 (s, 1H), 8.04 (s, 1H), 8.18 (d, 1H, J = 1.7 Hz), 9.37 (d, 1H, J = 1.7 Hz).

FAB-MS (m/z) ; 836(M+1)⁺

5 **Example 150 Synthesis of Compound 151**

The same procedure as in Example 9 was repeated using 81.7 mg (0.0978 mmol) of Compound 150 to give 65.9 mg (80%) of Compound 151.

10 FAB-MS (m/z) ; 840(M+1)⁺

Example 151 Synthesis of Compound 152

To a mixed solution of 56.5 mg (0.0673 mmol) of Compound 151 in methylene chloride (3 ml)/methanol (0.6 ml) was added 32.8 mg of potassium carbonate, followed by stirring at room temperature for 6 hours. The reaction mixture was poured into water, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give 33.4 mg (66%) of Compound 152.

15 ¹H-NMR (CDCl₃) δ; 2.14 (s, 3H), 2.80 (dd, 1H, J = 4.8, 14.4 Hz), 3.37 (d, 2H, J = 7.8 Hz), 3.41-3.47 (m, 2H), 3.53 (dd, 1H, J = 6.8, 14.2 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 3.75 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.95 (m, 1H), 4.09 (s, 3H), 4.67 (d, 1H, J = 16.6 Hz), 4.73 (d, 1H, J = 16.6 Hz), 5.11 (br, 1H), 5.42 (s, 1H), 6.77 (dd, 1H, J = 4.8, 7.6 Hz), 7.14 (m, 1H), 7.18 (d, 1H, J = 8.3 Hz), 7.29 (m, 1H), 7.82 (d, 1H, J = 8.8 Hz), 7.88 (d, 1H, J = 1.5 Hz), 8.69 (m, 1H).

20 FAB-MS (m/z) ; 756 (M+1)⁺

Example 152 Synthesis of Compound 153

To a solution of 10 mg (0.016 mmol) of Compound 122 in 3 ml of methanol was added 10 mg of 10% Pd/C, followed by reflux in a hydrogen atmosphere for a day. Insoluble materials were

removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give 2.7 mg (27%) of Compound 153.

1H-NMR (CDCl₃) δ ; 0.97 (t, 3H, J = 7.3 Hz), 1.40-1.47 (m, 2H), 1.67-1.78 (m, 2H), 2.19
5 (s, 3H), 2.35 (dd, 1H, J = 4.7, 14.5 Hz), 2.83 (t, 2H, J = 7.8 Hz), 3.23 - 3.31 (m,
5H), 4.08 (s, 3H), 4.88 (d, 2H, J = 1.7 Hz), 5.98 (br, 1H), 6.84 (dd, 1H, J = 4.7,
7.3 Hz), 7.16 (d, 1H, J = 7.7 Hz), 7.26 - 7.36 (m, 4H), 7.60 (ddd, 1H, J = 2.0, 5.9,
7.7 Hz), 7.68 - 7.73 (m, 3H), 8.61 (d, 1H, J = 4.0 Hz), 9.04 (br s, 1H).

10 FAB-MS (m/z); 629 (M+1)+

Example 153 Synthesis of Compound 154

To a solution of 67.9 mg (0.117 mmol) of Compound e in 3 ml of dichloromethane was added 0.02 ml (0.26 mmol) of chloromethyl methyl ether and 0.02 ml (0.12 mmol) of N,N-
15 diisopropylethylamine, and the mixture was stirred at room temperature for 8 hours. After addition of 1N aqueous solution of sodium hydroxide, the reaction mixture was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was triturated with methanol to give 53.8 mg (74%) of diacetylated Compound 154.

20 1H-NMR(CDCl₃) δ ; 1.80 (s, 3H), 2.16 (dd, 1H, J = 5.0, 14.6 Hz), 2.28 (s, 3H), 2.86 (s,
3H), 3.49 (s, 3H), 3.99 (dd, 1H, J = 7.5, 14.6 Hz), 4.01 (s, 3H), 4.80 (s, 2H), 4.86
(s, 2H), 5.41 (d, 1H, J = 17.6 Hz), 5.46 (d, 1H, J = 17.6 Hz), 7.02 (dd, 1H, J =
5.0, 7.5 Hz), 7.44 (m, 1H), 7.54 (m, 2H), 7.61 (m, 1H), 7.94 (d, 1H, J = 8.6 Hz),
25 8.09 (m, 1H), 9.23 (m, 1H).

FAB-MS (m/z) ; 625 (M)+

30 The same procedure as in Example 1, Step B, was repeated using 51.2 mg (0.0819 mmol) of diacetylated Compound 154 to give 39.2 mg (88%) of Compound 154.

1H-NMR(CDCl₃) δ ; 2.18 (s, 3H), 2.74 (dd, 1H, J = 4.9, 14.4 Hz), 3.46 (dd, 1H, J = 7.5, 14.4 Hz), 3.51 (s, 3H), 4.09 (s, 3H), 4.67 (d, 1H, J = 16.4 Hz), 4.75 (s, 2H), 4.78 (d, 1H, J = 16.4 Hz), 4.80 (s, 2H), 4.88 (s, 1H), 6.46 (s, 1H), 6.81 (dd, 1H, J = 4.9, 7.5 Hz), 7.29 (d, 1H, J = 8.3 Hz), 7.39 (m, 1H), 7.41 (m, 1H), 7.51 (m, 1H), 7.92 (m, 2H), 8.93 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z) ; 541 (M)+

10 **Example 154** **Synthesis of Compound 155**

The procedure as in Example 153 was repeated using 49.1 mg (0.0804 mmol) of Compound f to give 24.8 mg (44%) of diacetylated Compound 155.

15 1H-NMR(CDCl₃) δ ; 1.81 (s, 3H), 2.17 (dd, 1H, J = 5.0, 14.4 Hz), 2.26 (s, 3H), 2.87 (s, 3H), 3.49 (s, 3H), @3.50 (s, 3H), 3.99 (dd, 1H, J = 7.5, 14.4 Hz), 4.01 (s, 3H), 4.80 (s, 2H), 4.83 (s, 2H), 4.84 (s, 2H), 4.86 (s, 3H), 5.43 (d, 1H, J = 17.6 Hz), 5.48 (d, 1H, J = 17.6 Hz), 7.02 (dd, 1H, J = 5.0, 7.5 Hz), 7.55 (m, 1H), 7.62 (m, 1H), 7.92 (m, 2H), 8.06 (d, 1H, J = 1.2 Hz), 9.23 (d, 1H, J = 1.0 Hz).

20 FAB-MS (m/z) ; 699 (M) +

The same procedure as in Example 1, Step B, was repeated using 24.8 mg (0.0355 mmol) of diacetylated Compound 155 to give 19.9 mg (71%) of Compound 155.

25 1H-NMR(CDCl₃) δ ; 2.20 (s, 3H), 2.45 (dd, 1H, J = 4.9, 14.4 Hz), 3.34 (dd, 1H, J = 7.5, 14.4 Hz), 3.49 (s, 3H), 3.50 (s, 3H), 3.50 (s, 3H), 4.10 (s, 3H), 4.18 (s, 3H), 4.18 (s, 1H), 4.80 (s, 6H), 4.82 (s, 2H), 4.89 (d, 1H, J = 15.8 Hz), 4.96 (d, 1H, J = 15.8 Hz), 5.87 (s, 1H), 6.87 (dd, 1H, J = 4.9, 7.5 Hz), 7.41 (d, 1H, J = 8.6 Hz), 7.49 (m, 2H), 7.82 (d, 1H, J = 8.8 Hz), 7.90 (d, 1H, J = 1.5 Hz), 9.16 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z) ; 615 (M)+

Example 155 Synthesis of Compound 156

5 The procedure as in Example 153 was repeated using 46.0 mg (0.0753 mmol) of Compound f and 0.02 ml (0.22 mmol) of chloromethyl ethyl ether to give 50.9 mg (94%) of diacetylated Compound 156.

10 $^1\text{H-NMR}(\text{CDCl}_3) \delta$; 1.17 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.81 (s, 3H), 2.17 (dd, 1H, J = 5.1, 14.4 Hz), 2.26 (s, 3H), 2.86 (s, 3H), 3.74 (q, 2H, J = 7.1 Hz), 3.75 (q, 2H, J = 7.1 Hz), 3.98 (dd, 1H, J = 7.3, 14.4 Hz), 4.01 (s, 3H), 4.85 (s, 2H), 4.85 (s, 2H), 4.87 (s, 2H), 4.88 (s, 3H), 5.42 (d, 1H, J = 17.6 Hz), 5.47 (d, 1H, J = 17.6 Hz), 7.01 (dd, 1H, J = 5.1, 7.3 Hz), 7.54 (m, 2H), 7.61 (m, 1H), 7.90 (d, 1H, J = 8.6 Hz), 8.05 (d, 1H, J = 1.7 Hz), 9.23 (m, 1H).

15 FAB-MS (m/z) ; 727 (M)+

The same procedure as in Example 1, Step B, was repeated using 50.9 mg (0.0700 mmol) of diacetylated Compound 156 to give 23.1 mg (51%) of Compound 156.

20 $^1\text{H-NMR}(\text{CDCl}_3) \delta$; 1.30 (t, 6H, J = 7.1 Hz), 2.20 (s, 3H), 2.41 (dd, 1H, J = 4.9, 14.4 Hz), 3.32 (dd, 1H, J = 7.6, 14.4 Hz), 3.73 (q, 2H, J = 7.1 Hz), 3.73 (q, 2H, J = 7.1 Hz), 4.08 (s, 1H), 4.10 (s, 3H), 4.81 (s, 2H), 4.83 (s, 2H), 4.85 (s, 4H), 4.91 (d, 1H, J = 16.8 Hz), 4.98 (d, 1H, J = 16.8 Hz), 5.91 (s, 1H), 6.88 (dd, 1H, J = 4.9, 7.6 Hz), 7.42 (d, 1H, J = 8.3 Hz), 7.49 (m, 2H), 7.81 (d, 1H, J = 8.5 Hz), 7.90 (d, 1H, J = 1.2 Hz), 9.18 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z) ; 643 (M)+

30 **Example 156 Synthesis of Compound 157**

To a solution of 45.0 mg (0.0854 mmol) of Compound h in 2 ml of dichloromethane was added 0.1 ml (1.3 mmol) of 2-methoxyethanol and 36.2 mg (0.156 mmol) of (\pm) 10-camphorsulfonic acid, and the mixture was stirred at room temperature for 2 days. After addition of saturated aqueous solution of sodium bicarbonate, the reaction mixture was extracted with 5 chloroform. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC (chloroform/methanol = 95/5) to give 19.9 mg (36%) of Compound 157.

10 $^1\text{H-NMR}(\text{CDCl}_3)$ δ ; 2.19 (s, 3H), 2.42 (dd, 1H, J = 4.6, 14.3 Hz), 3.32 (dd, 1H, J = 7.2, 14.3 Hz), 3.41 (s, 3H), 3.43 (s, 3H), 3.60-3.64 (m, 4H), 4.09 (s, 3H), 4.17 (br, 1H), 4.77 (s, 2H), 4.80 (s, 2H), 4.89 (d, 1H, J = 16.6 Hz), 4.97 (d, 1H, J = 16.6 Hz), 5.95 (br, 1H), 6.87 (dd, 1H, J = 4.6, 7.2 Hz), 7.43 (d, 1H, J = 8.5 Hz), 7.47 (m, 1H), 7.53 (d, 1H, J = 8.5 Hz), 7.85 (d, 1H, J = 8.5 Hz), 7.91 (s, 1H), 9.10 (s, 1H).

15

FAB-MS (m/z) ; 643 (M) +

Reference Example 1 Synthesis of Compound A

20 To a solution of 5.00 g (9.07 mmol) of Compound c (Japanese Published Unexamined Patent Application No. 295588/88) in 100 ml of a 10% methanol/chloroform mixture was added 1.62 g (9.10 mmol) of N-bromosuccinimide under ice cooling, followed by stirring at room temperature for 8.5 hours. The precipitated crystals were separated by filtration and dried to give 3.59 g (63%) of Compound A.

25

1 H-NMR (CDCl_3) δ ; 1.82 (s, 3H), 2.18 (dd, 1H, J = 5.1, 14.5 Hz), 2.30 (s, 3H), 2.83 (s, 3H), 4.00 (dd, 1H, J = 7.5, 14.5 Hz), 4.03 (s, 3H), 5.40 (d, 1H, J = 17.5 Hz), 5.44 (d, 1H, J = 17.5 Hz), 6.98 (dd, 1H, J = 5.1, 7.5 Hz), 7.44 (d, 1H, J = 8.7 Hz), 7.47 (m, 1H), 7.57 (m, 1H), 7.64 (dd, 1H, J = 2.0, 8.7 Hz), 7.96 (d, 1H, J = 8.4 Hz), 30 8.10 (m, 1H), 9.39 (d, 1H, J = 2.0 Hz).

FAB-MS (m/z) ; 630 (M)⁺, 632 (M+2)⁺

Reference Example 2 **Synthesis of Compound B**

A solution of 501 mg (0.794 mmol) of Compound A and 111 mg (0.792 mmol) of
5 hexamethylenetetramine in 5 ml of trifluoroacetic acid was stirred under reflux for 4 hours, followed
by addition of water. Resulting insoluble materials were collected by filtration, purified by silica gel
column chromatography (chloroform/methanol = 99/1) and then by methanol trituration to give 296
mg (57%) of Compound B.

10 ¹H-NMR (DMSO-d₆) δ; 1.70 (s, 3H), 2.25 (s, 3H), 2.32 (dd, 1H, J = 5.0, 14.8 Hz), 2.68
 (s, 3H), 3.90 (dd, 1H, J = 7.5, 14.8Hz), 3.96 (s, 3H), 5.44 (d, 1H, J = 17.7 Hz),
 5.49 (d, 1H, J = 17.7 Hz), 7.35 (dd, 1H, J = 5.0, 7.5 Hz), 7.69 (m, 1H), 8.05 (d,
 1H, J = 8.8 Hz), 8.13 (m, 1H), 8.21 (d, 1H, J = 8.7 Hz), 8.67 (m, 1H), 9.24 (d, 1H,
 J = 1.9 Hz), 10.24 (s, 1H).

15 FAB-MS (m/z) ; 658 (M)⁺ , 660 (M+2)⁺

Reference Example 3 **Synthesis of Compound C**

Compound B (237 mg, 0.360 mmol), 64.2 mg (0.0556 mmol) of
20 tetrakis(triphenylphosphine) palladium and 44.6 mg (0.454 mmol) of potassium acetate were
dissolved in 2 ml of N,N-dimethylformamide, and the solution was stirred at 100°C for 2 hours. To
the reaction mixture was added water, followed by extraction with chloroform. The extract was
washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium
sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by silica
25 gel column chromatography (chloroform/methanol = 99/1) to give 71.2 mg (34%) of Compound C.

30 ¹H-NMR (CDCl₃) δ; 1.79 (s, 3H), 2.15 (dd, 1H, J = 5.1, 14.7 Hz), 2.25 (s, 3H), 2.71 (s,
 3H), 4.00 (dd, 1H, J = 7.7, 14.7Hz), 4.02 (s, 3H), 5.30 (s, 2H), 7.02 (dd, 1H, J =
 5.1, 7.7 Hz), 7.34 (m, 1H), 7.54 (m, 2H), 8.01 (d, 1H, J = 8.8 Hz), 8.08 (m, 1H),
 9.43 (d, 1H, J = 1.2 Hz), 9.16 (d, 1H, J = 8.1 Hz), 10.19 (s, 1H).

FAB-MS (m/z) ; 580 (M+1)⁺

Reference Example 4 **Synthesis of Compound D**

To a solution of 1.02 g of Compound c (Japanese Published Unexamined Patent Application No. 295588/88) in 50 ml of 1,2-dichloroethane was added dropwise 0.17 ml of fuming nitric acid, and the mixture was stirred at room temperature for 10 minutes. A saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol = 99/1) to give 537 mg (49%) of Compound D.

¹H-NMR (CDCl₃) δ; 1.82 (s, 3H), 2.26 (dd, 1H, J = 5.4, 14.6 Hz), 2.31 (s, 3H), 2.70 (s, 3H), 4.03 (s, 3H), 4.07 (dd, 1H, J = 7.5, 14.6 Hz), 5.38 (s, 2H), 6.99 (dd, 1H, J = 5.4, 7.5 Hz), 7.48 - 7.59 (m, 3H), 7.96 - 8.08 (m, 2H), 8.03 (m, 1H), 10.02 (s, 1H).

FAB-MS (m/z) ; 597 (M+1)⁺

Reference Example 5 **Synthesis of Compound E**

A solution of 50.0 mg (0.0839 mmol) of Compound D and 175 mg (1.25 mmol) of hexamethylenetetramine in 1 ml of trifluoroacetic acid was stirred under reflux for 2 hours. After addition of water, the reaction mixture was neutralized with a saturated aqueous solution of sodium hydrogen carbonate, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave Compound E.

¹H-NMR (CDCl₃) δ; 1.83 (s, 3H), 2.29 (dd, 1H, J = 5.3, 14.7 Hz), 2.34 (s, 3H), 2.64 (s, 3H), 4.05 (s, 3H), 4.12 (dd, 1H, J = 7.5, 14.7 Hz), 5.34 (d, 1H, J = 17.6 Hz), 5.40 (d, 1H, J = 17.6 Hz), 7.02 (dd, 1H, J = 5.3, 7.5 Hz), 7.54 (d, 1H, J = 9.3 Hz), 8.07 (d, 1H, J = 8.6 Hz), 8.15 (m, 1H), 8.37 (m, 1H), 8.50 (d, 1H, J = 1.5 Hz), 8.90 (d, 1H, J = 2.2 Hz), 10.24 (s, 1H).

FAB-MS (m/z) ; 625 (M+1)⁺

Reference Example 6 **Synthesis of Compound F**

Methanol (3 ml) was added to 1.4 g (60-65%, ca. 2.6 mmol) of mercury (II) nitrate monohydrate, followed by stirring at room temperature for 5 minutes. To the mixture were successively added a solution of 551 mg (1.0 mmol) of Compound c (Japanese Published Unexamined Patent Application No. 295588/88) in 12 ml of chloroform and 660 mg (2.6 mmol) of iodine, and the resulting mixture was stirred at room temperature for one hour. The reaction mixture was poured into 150 ml (1 N) of an aqueous solution of sodium thiosulfate, followed by extraction with chloroform. The extract was washed with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (chloroform) to give 750 mg (93%) of Compound F.

15 ¹H-NMR (CDCl₃) δ; 2.14 (s, 3H), 3.00 (dd, 1H, J = 4.6, 14.5 Hz), 3.72 (dd, 1H, J = 4.6, 7.6 Hz), 4.09 (s, 3H), 4.31 (d, 1H, J = 16.6), 4.59 (d, 1H, J = 16.6 Hz), 5.39 (br, 1H), 5.54 (br, 1H), 6.78 (dd, 1H, J = 6.0, 7.6 Hz), 7.13 (d, 1H, J = 8.5 Hz), 7.45 (dd, 1H, J = 1.7, 8.5 Hz), 7.72 (d, 1H, J = 8.7 Hz), 7.76 (dd, 1H, J = 1.7, 8.7 Hz), 8.16 (d, 1H, J = 1.5 Hz), 8.83 (d, 1H, J = 1.0 Hz).

FAB-MS (m/z) ; 804 (M+1)⁺

20

Reference Example 7 **Synthesis of Compound G**

The same procedure as in Reference Example 6 was repeated using 23.4 mg (0.05 mmol) of K-252a to give 11 mg (86%) of Compound G.

25 ¹H-NMR (CDCl₃) δ; 1.80 (s, 3H), 2.11 (dd, 1H, J = 7.3, 16.2 Hz), 2.24 (s, 3H), 2.79 (s, 3H), 3.97 (dd, 1H, J = 7.3, 9.3 Hz), 4.00 (s, 3H), 5.32 (m, 2H), 6.93 (dd, 1H, J = 2.7, 7.6 Hz), 7.27 (m, 1H), 7.68 (d, 1H, J = 8.8 Hz), 7.78 (m, 2H), 8.32 (br, 1H), 9.52 (br, 1H).

FAB-MS (m/z) ; 720 (M+1)⁺

Example 157 Spinal Cord ChAT Activity Assay

The effect of selected ring substituted K-252a derivatives on ChAT activity was assayed in
5 dissociated spinal cord cultures prepared from fetal rats using the procedure described in U.S.
Patent 5,461,146, Columns 26 and 27, Examples 6 and 7. ChAT is the enzyme that catalyzes the
synthesis of the neurotransmitter acetylcholine, and it is a specific biochemical marker for
cholinergic neurons. In the spinal cord, the large majority of cholinergic neurons are motor neurons.
Assay of this enzyme may thus be used as an indication of the effects of a factor, or factors, on the
10 survival of cholinergic neurons and/or regulation of this enzyme.

The compounds were tested at 30nM and 300nM, and the data are summarized in Table 3.
Compounds which increased ChAT activity at least 120% of the control activity are considered
active.

Table 3: Spinal Cord ChAT Activity

Compound #	ChAT Activity maximum efficacy % of Control (conc)
1	153 (30nM)
2	149 (300nM)
3	134 (300nM)
4	183 (300nM)
5	242 (300nM)
6	149 (2000nM)
7	186 (300nM)
8	150 (300nM)
9	<120
10	164 (300nM)
11	236 (300nM)
12	269 (300nM)
13	271 (30nM)
14	282 (300nM)
16	159 (300nM)
18	270 (300nM)
19	228 (300nM)
20	157 (300nM)
21	249 (30nM)
22	258 (100nM)
23	233 (100nM)
34	<120
41	204 (300nM)
42a	151 (300nM)
44	<120
47	<120
52	<120
54	<120
59	160 (300nM)
62	235 (300nM)
68	291 (300nM)
70b	169 (300nM)
70c	186 (300nM)
71	193 (300nM)
81	131 (300nM)
87	294 (300nM)
88	190 (300nM)
91	<120
92	210 (300nM)
94	152 (300nM)
95	272 (300nM)

116	231 (30nM)
117	232 (30nM)
118	249 (30nM)
119	272 (30nM)
120	257 (300nM)
122	279 (300nM)
139	<120
140	156 (300nM)
142	223 (300nM)
143	264 (300nM)
145	129 (300nM)
146	153 (300nM)
148	206 (300nM)
154	177(300nM)
155	197(300nM)
156	217 (300nM)

Example 158: Basal Forebrain ChAT Activity Assay

5 Compounds of the invention were assessed for their ability to promote survival and increase in ChAT activity in basal forebrain cultures. ChAT activity in these cultures is a biochemical marker for the cholinergic neurons (less than 5% of the cells in culture), which represent the major cholinergic input to the hippocampal formation, olfactory nucleus, interpeduncular nucleus, cortex, amygdala, and parts of the thalamus. Representative compounds of the invention not only increased 10 ChAT activity but in addition increased general survival of neurons in basal forebrain cultures.

The basal forebrain was dissected from embryonic day 17 or 18 rat embryos and the cells were dissociated with Dispase™ (neutral protease, Collaborative Research). Neurons were plated at 5 x 10⁴ cells/well (1.5 x 10⁵ cells/cm²) in wells of 96-well plates previously coated with poly-l-ornithine and laminin. Cells were cultured in serum-free N₂ medium containing 0.05% bovine 15 serum albumin (BSA) (Bottenstein et al., *supra*) at 37° in a humidified atmosphere of 5% CO₂/95% air. ChAT activity was measured *in vitro* at day six, using a modification of the Fonnun procedure (supra) according to McManaman et al. (*supra*) and Glicksman et al. (*J. Neurochem.* 61:210-221, 1993).

20 The compounds were tested at concentrations between 10nM and 500nM, and the data are summarized in Table 4. Compounds which increased ChAT activity at least 120% of the control activity are considered active.

Table 4: Basal Forebrain ChAT Activity

Compound #	ChAT Activity maximum efficacy % of Control (conc)
7	<120
8	144 (100nM)
11	149 (250nM)
12	184 (500nM)
13	167 (100nM)
14	229 (500nM)
16	143 (100nM)
18	148 (250nM)
19	172 (100nM)
20	176 (500nM)
21	171 (50nM)
22	174 (50nM)
23	134 (50nM)
34	145 (500nM)
41	<120
42a	246 (250nM)
42b	164 (250nM)
44	<120
45	<120
46	<120
47	<120
48	<120
49	<120
52	<120
54	167 (250nM)
59	131 (250nM)
61	166 (50nM)
62	202 (50nM)
64	165 (250nM)
68	290 (250nM)
70a	<120
70b	239 (250nM)
70c	203 (250nM)
71	152 (250nM)
73b	171 (250nM)
73c	190 (250nM)
75	<120
76	<120

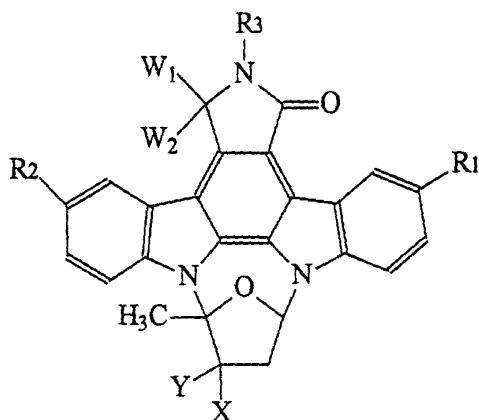
77	132 (250nM)
78	<120
79	<120
80	<120
81	<120
82	150 (250nM)
83	<120
84	<120
87	262 (250nM)
88	<120
89	<120
90	<120
91	<120
92	311 (250nM)
93	<120
94	166 (250nM)
95	239 (250nM)
96	<120
99	136 (50nM)
102	176 (50nM)
103	154 (50nM)
104	<120
105	136 (50nM)
106	135 (250nM)
107	<120
108	<120

Those skilled in the art will appreciate that numerous changes and modifications may be made to the preferred embodiments of the invention and that such changes and modifications may be made without departing from the spirit of the invention. It is therefore intended that the appended claims cover all equivalent variations as fall within the true spirit and scope of the invention.

5 Documents cited throughout this patent disclosure are hereby incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound defined by the general formula (I):



wherein:

one of R¹ and R² is selected from the group consisting of:

a) -CO(CH₂)_jR⁴, wherein j is 1 to 6, and R⁴ is selected from the group consisting of:

- 1) [hydrogen] and a halogen;
- 2) -NR⁵R⁶, wherein R⁵ and R⁶ independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted aralkyl, unsubstituted aralkyl, lower alkylaminocarbonyl, or lower alkoxy carbonyl; or R⁵ and R⁶ are combined with a nitrogen atom to form a heterocyclic group;
- 3) N₃;
- 4) -SR²⁷, wherein R²⁷ is selected from the group consisting of:
 - i) hydrogen;
 - ii) substituted lower alkyl;
 - iii) unsubstituted lower alkyl;
 - iv) substituted aryl;
 - v) unsubstituted aryl;
 - vi) substituted heteroaryl;
 - vii) unsubstituted heteroaryl;

viii) substituted aralkyl;

ix) unsubstituted aralkyl;

x) thiazolinyl;

xi) $-(CH_2)_aCO_2R^{28}$, wherein a is 1 or 2, and R^{28} is selected from the group consisting of: hydrogen and lower alkyl; and

xii) $-(CH_2)_aCONR^5R^6$; and

5) OR^{29} (wherein R^{29} is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, or COR^{30} (wherein R^{30} is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl));

b) $-CH(OH)(CH_2)_bR^{4A}$, wherein b is 1 to 6 and R^{4A} is hydrogen or the same as R^4 ;

c) $-(CH_2)_dCHR^{31}CO_2R^{32}$ wherein d is 0 to 5, R^{31} is hydrogen, $-CONR^5R^6$, or CO_2R^{33} (wherein R^{33} is hydrogen or lower alkyl), and R^{32} is hydrogen or lower alkyl;

d) $-(CH_2)_dCHR^{31}CONR^5R^6$;

e) $-(CH_2)_kR^7$ wherein k is 2 to 6, and R^7 is halogen, CO_2R^8 (wherein R^8 is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl), $CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^9 (wherein R^9 is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, substituted aryl, or unsubstituted aryl), SR^{27B} (wherein R^{27B} is the same as R^{27}), $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are the same as R^5 and R^6) or N_3 ;

f) $-CH=CH(CH_2)_mR^{12}$ wherein m is 0 to 4, and R^{12} is hydrogen, lower alkyl, CO_2R^{8A} (wherein R^{8A} is the same as R^8), $-CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^{9A} (wherein R^{9A} is the same as R^9), or $NR^{10A}R^{11A}$ (wherein R^{10A} and R^{11A} are the same as R^5 and R^6);

g) $-CH=C(CO_2R^{33A})_2$, wherein R^{33A} is the same as R^{33} ;

h) $-C\equiv C(CH_2)_nR^{13}$, wherein n is 0 to 4, and R^{13} is the same as R^{12} ;

i) $-CH_2OR^{44}$, wherein R^{44} is substituted lower alkyl;

and the other of R^1 or R^2 is selected from the group consisting of

j) hydrogen, lower alkyl, halogen, acyl, nitro, $NR^{14}R^{15}$ (wherein R^{14} or R^{15} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

- k) $-\text{CH}(\text{SR}^{34})_2$, wherein R^{34} is lower alkyl or alkylene;
- l) $-\text{CH}_2\text{R}^{35}$, wherein R^{35} is OR^{36} (wherein R^{36} is tri-lower alkyl silyl in which the three lower alkyl groups are the same or different, or is the same as R^{29}), or SR^{37} (wherein R^{37} is the same as R^{27});
- m) $-\text{CO}(\text{CH}_2)_q\text{R}^{16}$, wherein q is 1 to 6, and R^{16} is the same as R^4 ;
- n) $-\text{CH}(\text{OH})(\text{CH}_2)_e\text{R}^{38}$, wherein e is 1 to 6, and R^{38} is the same as R^{4A} ;
- o) $-(\text{CH}_2)_f\text{CHR}^{39}\text{CO}_2\text{R}^{40}$, wherein f is 0 to 5, R^{39} is the same as R^{31} and R^{40} is the same as R^{32} ;
- p) $-(\text{CH}_2)_r\text{R}^{17}$, wherein r is 2 to 6, and R^{17} is the same as R^7 ;
- q) $-\text{CH}=\text{CH}(\text{CH}_2)_t\text{R}^{18}$, wherein t is 0 to 4, and R^{18} is the same as R^{12} ;
- r) $-\text{CH}=\text{C}(\text{CO}_2\text{R}^{33B})_2$, wherein R^{33B} is the same as R^{33} ;
- s) $-\text{C}\equiv\text{C}(\text{CH}_2)_u\text{R}^{19}$, wherein u is 0 to 4, and R^{19} is the same as R^{13});

R^3 is hydrogen, acyl, or lower alkyl;

X is selected from the group consisting of:

- a) hydrogen;
- b) formyl;
- c) lower alkoxy carbonyl;
- d) $-\text{CONR}^{20}\text{R}^{21}$, wherein:

R^{20} and R^{21} independently are:

hydrogen;

lower alkyl;

$-\text{CH}_2\text{R}^{22}$, wherein R^{22} is hydroxy, or

$-\text{NR}^{23}\text{R}^{24}$ (wherein R^{23} or R^{24} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, or the residue of an α -amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{23} and R^{24} are combined with a nitrogen atom to form a heterocyclic group); and

- e) $-\text{CH}=\text{N}-\text{R}^{25}$, wherein R^{25} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

Y is hydroxy, lower alkoxy, aralkyloxy, or acyloxy; or

X and Y combined represent, $-\text{X}-\text{Y}-$, $=\text{O}$, $-\text{CH}_2\text{O}(\text{C}=\text{O})\text{O}-$, $-\text{CH}_2\text{OC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{NR}^{26}\text{C}(\text{=O})-$ (wherein R^{26} is hydrogen or lower alkyl), $-\text{CH}_2\text{NHC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{OS}(\text{=O})\text{O}-$, or $-\text{CH}_2\text{OC}(\text{CH}_3)_2\text{O}-$; and

W¹ and W² are hydrogen, or W¹ and W² together represent oxygen; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein:

a) one of R¹ and R² is selected from the group consisting of -(CH₂)_kR⁷, -CH=CH(CH₂)_mR¹², -C≡C(CH₂)_nR¹³, -CO(CH₂)_jSR²⁷ and -CH₂OR⁴⁴, wherein R⁴⁴ is methoxymethyl, ethoxymethyl, or methoxyethyl;

and the other of R¹ and R² is selected from the group consisting of

-(CH₂)_rR¹⁷, -CH=CH(CH₂)_tR¹⁸, -C≡C(CH₂)_uR¹⁹, NR¹⁴R¹⁵, hydrogen, halogen, nitro, -CH₂O-, substituted lower alkyl, unsubstituted lower alkyl, -CO(CH₂)_qSR²⁷, -CH₂R³⁵, wherein R³⁵ is OR³⁶, and -CH₂SR³⁷, wherein R³⁷ is selected from the group consisting of lower alkyl, pyridyl, and benzimidazole;

b) k and r are each 2, 3, or 4;
c) j and q are each 1 or 2;
d) R⁷ and R¹⁷ are:

1) selected independently from the group consisting of : phenyl, pyridyl, imidazolyl, thiazolyl, or tetrazolyl; or

2) selected pairwise, from the group consisting of:

i) -CO₂R⁸ and CO₂R^{8A}, where R⁸ and R^{8A}, independently, are hydrogen, methyl, ethyl, or phenyl;
ii) -OR⁹ and -OR^{9A}, where R⁹ and R^{9A}, independently, are hydrogen, methyl, ethyl, phenyl, or acyl;
iii) -SR^{27B}, where R^{27B} is selected from the group consisting of unsubstituted lower alkyl, 2-thiazoline, and pyridyl; and
iv) -NR¹⁰R¹¹ and -NR¹⁴R¹⁵, where R¹⁰, R¹¹, R¹⁴, and R¹⁵, independently, are selected from the group consisting of hydrogen, methyl, ethyl, phenyl, carbamoyl, and lower alkylaminocarbonyl;

e) R²⁷ is selected from the group consisting of substituted lower alkyl, unsubstituted lower alkyl, substituted phenyl, unsubstituted phenyl, pyridyl, pyrimidinyl, thiazole, and tetrazole;

- f) R^{36} is selected from the group consisting of methoxymethyl, ethoxymethyl, and methoxyethyl;
- g) m, n, t and u each is 0 or 1; and
- h) R^{12}, R^{13}, R^{18} , and R^{19} are independently selected from the group consisting of hydrogen, methyl ethyl, phenyl, pyridyl, imidazole, thiazole, tetrazole, $-CO_2R^8$, $-OR^9$, and $NR^{10}R^{11}$, wherein R^8, R^9, R^{10} , and R^{11} each is hydrogen, methyl, ethyl, or phenyl.

3. The compound of claim 2, wherein R^3 is hydrogen or acetyl, X is hydroxymethyl or lower alkoxycarbonyl, Y is hydroxy or acetoxy, and W^1 and W^2 are hydrogen.

4. The compound of claim 3, wherein X is methoxycarbonyl, Y is hydroxy, and R^3 is hydrogen.

5. The compound of claim 3 wherein:

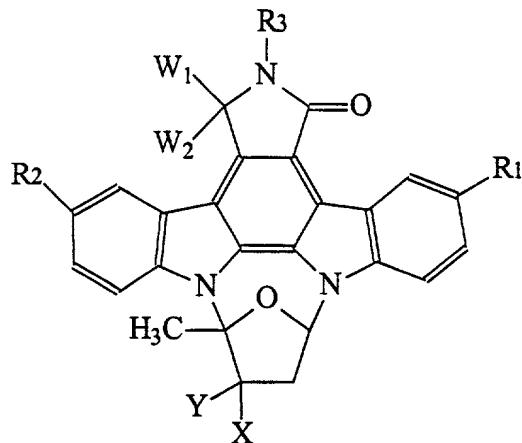
one of R^1 and R^2 is selected from the group consisting of methoxycarbonylvinyl, ethoxycarbonylvinyl, styryl, 2-pyridylvinyl, 4-pyridylvinyl, 2-pyridylethyl, 4-pyridylethyl, phenylethyl, methoxypropynyl, hydroxypropynyl, $-COCH_2SEt$, $-C\equiv CCH_2NMeBn$, $-CH=CHEt$, $-(CH_2)_2SMe$, $-(CH_2)_2S-2-thiazoline$, $-(CH_2)_3SMe$, $-CH=CHEt$, $-CH=CH-2-imidazole$, $(CH_2)_2OC(=O)H$, methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, and 2-hydroxyethyl;

and the other of R^1 and R^2 is selected from the group

consisting of hydrogen, halogen, methoxycarbonylvinyl, ethoxycarbonylvinyl, styryl, 2-pyridylvinyl, 4-pyridylvinyl, 2-pyridylethyl, 4-pyridylethyl, phenylethyl, nitro, amino, N-ethylurea, methoxypropynyl, hydroxypropynyl, $-COCH_2SEt$, $-C\equiv CCH_2NMeBn$, $-CH=CHEt$, $-(CH_2)_2SMe$, $-(CH_2)_2S-2-thiazoline$, $-(CH_2)_3SMe$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SEt$, pyridylthiomethyl, $-CH_2S-2-benzimidazole$,

-CH=CHEt, -CH=CH-2-imidazole, -(CH₂)₂OC(=O)H, methoxymethoxymethyl, ethoxymethoxymethyl, methoxyethoxymethyl, and 2-hydroxyethyl.

6. A method for enhancing the function of a trophic factor responsive cell, comprising the step of contacting said cell with a compound defined by the general formula (I):



wherein:

one of R¹ and R² is selected from the group consisting of:

- a) -CO(CH₂)^jR⁴, wherein j is 1 to 6, and R⁴ is selected from the group consisting of:
 - 1) hydrogen and a halogen;
 - 2) -NR⁵R⁶, wherein R⁵ and R⁶ independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted aralkyl, unsubstituted aralkyl, lower alkylaminocarbonyl, or lower alkoxy carbonyl; or R⁵ and R⁶ are combined with a nitrogen atom to form a heterocyclic group;
 - 3) N₃;
 - 4) -SR²⁷, wherein R²⁷ is selected from the group consisting of:
 - i) hydrogen;
 - ii) substituted lower alkyl;
 - iii) unsubstituted lower alkyl;
 - iv) substituted aryl;

- v) unsubstituted aryl;
- vi) substituted heteroaryl;
- vii) unsubstituted heteroaryl;
- viii) substituted aralkyl;
- ix) unsubstituted aralkyl;
- x) thiazolinyl;
- xi) $-(CH_2)_aCO_2R^{28}$, wherein a is 1 or 2, and R^{28} is selected from the group consisting of: hydrogen and lower alkyl; and
- xii) $-(CH_2)_aCONR^5R^6$; and

5) OR^{29} (wherein R^{29} is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, or COR^{30} (wherein R^{30} is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl));

- b) $-CH(OH)(CH_2)_bR^{4A}$, wherein b is 1 to 6 and R^{4A} is hydrogen or the same as R^4 ;
- c) $-(CH_2)_dCHR^{31}CO_2R^{32}$ wherein d is 0 to 5, R^{31} is hydrogen, $-CONR^5R^6$, or CO_2R^{33} (wherein R^{33} is hydrogen or lower alkyl), and R^{32} is hydrogen or lower alkyl;
- d) $-(CH_2)_dCHR^{31}CONR^5R^6$;
- e) $-(CH_2)_kR^7$ wherein k is 2 to 6, and R^7 is halogen, CO_2R^8 (wherein R^8 is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl), $CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^9 (wherein R^9 is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, substituted aryl, or unsubstituted aryl), SR^{27B} (wherein R^{27B} is the same as R^{27}), $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are the same as R^5 and R^6) or N_3 ;
- f) $-CH=CH(CH_2)_mR^{12}$ wherein m is 0 to 4, and R^{12} is hydrogen, lower alkyl, CO_2R^{8A} (wherein R^{8A} is the same as R^8), $-CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^{9A} (wherein R^{9A} is the same as R^9), or $NR^{10A}R^{11A}$ (wherein R^{10A} and R^{11A} are the same as R^5 and R^6);
- g) $-CH=C(CO_2R^{33A})_2$, wherein R^{33A} is the same as R^{33} ;
- h) $-C\equiv C(CH_2)_nR^{13}$, wherein n is 0 to 4, and R^{13} is the same as R^{12} ;
- i) $-CH_2OR^{44}$, wherein R^{44} is substituted lower alkyl;

and the other of R^1 or R^2 is selected from the group consisting of

j) hydrogen, lower alkyl, halogen, acyl, nitro, $NR^{14}R^{15}$ (wherein R^{14} or R^{15} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

k) $-CH(SR^{34})_2$, wherein R^{34} is lower alkyl or alkylene;

l) $-CH_2R^{35}$, wherein R^{35} is OR^{36} (wherein R^{36} is tri-lower alkyl silyl in which the three lower alkyl groups are the same or different, or is the same as R^{29}), or SR^{37} (wherein R^{37} is the same as R^{27});

m) $-CO(CH_2)_qR^{16}$, wherein q is 1 to 6, and R^{16} is the same as R^4 ;

n) $-CH(OH)(CH_2)_eR^{38}$, wherein e is 1 to 6, and R^{38} is the same as R^{4A} ;

o) $-(CH_2)_fCHR^{39}CO_2R^{40}$, wherein f is 0 to 5, R^{39} is the same as R^{31} and R^{40} is the same as R^{32} ;

p) $-(CH_2)_rR^{17}$, wherein r is 2 to 6, and R^{17} is the same as R^7 ;

q) $-CH=CH(CH_2)_tR^{18}$, wherein t is 0 to 4, and R^{18} is the same as R^{12} ;

r) $-CH=C(CO_2R^{33B})_2$, wherein R^{33B} is the same as R^{33} ;

s) $-C\equiv C(CH_2)_uR^{19}$, wherein u is 0 to 4, and R^{19} is the same as R^{13});

R^3 is hydrogen, acyl, or lower alkyl;

X is selected from the group consisting of:

a) hydrogen;

b) formyl;

c) lower alkoxy carbonyl;

d) $-CONR^{20}R^{21}$, wherein:

R^{20} and R^{21} independently are:

hydrogen;

lower alkyl;

$-CH_2R^{22}$, wherein R^{22} is hydroxy, or

$-NR^{23}R^{24}$ (wherein R^{23} or R^{24} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, or the residue of an α -amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{23} and R^{24} are combined with a nitrogen atom to form a heterocyclic group); and

e) $-CH=N-R^{25}$, wherein R^{25} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

Y is hydroxy, lower alkoxy, aralkyloxy, or acyloxy; or

X and Y combined represent, -X-Y-, =O, -CH₂O(C=O)O-, -CH₂OC(=S)O-, -CH₂NR²⁶C(=O)- (wherein R²⁶ is hydrogen or lower alkyl), -CH₂NHC(=S)O-, -CH₂OS(=O)O-, or -CH₂OC(CH₃)₂O-; and

W¹ and W² are hydrogen, or W¹ and W² together represent oxygen; or a pharmaceutically acceptable salt thereof.

7. A method for enhancing the function of a trophic factor responsive cell, comprising the step of contacting said cell with at least one compound of claim 2.

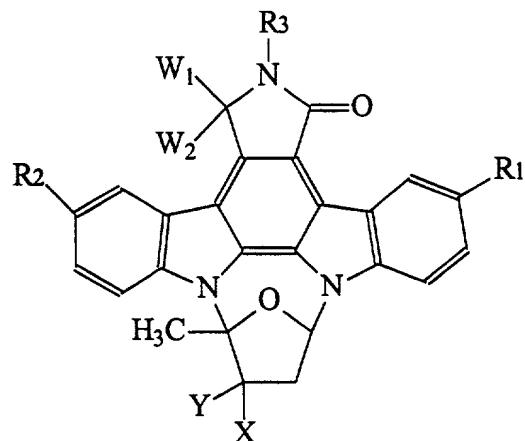
8. A method for enhancing the function of a trophic factor responsive cell, comprising the step of contacting said cell with at least one compound of claim 5.

9. The method of claim 6, wherein said trophic factor responsive cell is in a mammal.

10. The method of claim 6, wherein said trophic factor responsive cell is a neuron.

11. The method of claim 10, wherein said neuron is selected from the group consisting of cholinergic neurons and sensory neurons.

12. A method for enhancing the survival of a trophic factor responsive cell, comprising the step of contacting said cell with a compound defined by the general formula (I):



wherein:

one of R¹ and R² is selected from the group consisting of:

- a) -CO(CH₂)_jR⁴, wherein j is 1 to 6, and R⁴ is selected from the group consisting of:
 - 1) hydrogen and a halogen;
 - 2) -NR⁵R⁶, wherein R⁵ and R⁶ independently are hydrogen, substituted lower alkyl, unsubstituted lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, substituted aralkyl, unsubstituted aralkyl, lower alkylaminocarbonyl, or lower alkoxy carbonyl; or R⁵ and R⁶ are combined with a nitrogen atom to form a heterocyclic group;
 - 3) N₃;
 - 4) -SR²⁷, wherein R²⁷ is selected from the group consisting of:
 - i) hydrogen;
 - ii) substituted lower alkyl;
 - iii) unsubstituted lower alkyl;
 - iv) substituted aryl;
 - v) unsubstituted aryl;
 - vi) substituted heteroaryl;
 - vii) unsubstituted heteroaryl;
 - viii) substituted aralkyl;
 - ix) unsubstituted aralkyl;
 - x) thiazolinyl;
 - xi) -(CH₂)_aCO₂R²⁸, wherein a is 1 or 2, and R²⁸ is selected from the group consisting of: hydrogen and lower alkyl; and
 - xii) -(CH₂)_aCONR⁵R⁶; and
 - 5) OR²⁹ (wherein R²⁹ is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, or COR³⁰ (wherein R³⁰ is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl));
 - b) -CH(OH)(CH₂)_bR^{4A}, wherein b is 1 to 6 and R^{4A} is hydrogen or the same as R⁴;
 - c) -(CH₂)_dCHR³¹CO₂R³² wherein d is 0 to 5, R³¹ is hydrogen, -CONR⁵R⁶, or CO₂R³³ (wherein R³³ is hydrogen or lower alkyl), and R³² is hydrogen or lower alkyl;
 - d) -(CH₂)_dCHR³¹CONR⁵R⁶;
 - e) -(CH₂)_kR⁷ wherein k is 2 to 6, and R⁷ is halogen, CO₂R⁸ (wherein R⁸ is

hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl), CONR⁵R⁶, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR⁹ (wherein R⁹ is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl, substituted aryl, or unsubstituted aryl), SR^{27B} (wherein R^{27B} is the same as R²⁷), NR¹⁰R¹¹ (wherein R¹⁰ and R¹¹ are the same as R⁵ and R⁶) or N₃;

- f) -CH=CH(CH₂)_mR¹² wherein m is 0 to 4, and R¹² is hydrogen, lower alkyl, CO₂R^{8A} (wherein R^{8A} is the same as R⁸), -CONR⁵R⁶, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^{9A} (wherein R^{9A} is the same as R⁹), or NR^{10A}R^{11A} (wherein R^{10A} and R^{11A} are the same as R⁵ and R⁶);
- g) -CH=C(CO₂R^{33A})₂, wherein R^{33A} is the same as R³³;
- h) -C≡C(CH₂)_nR¹³, wherein n is 0 to 4, and R¹³ is the same as R¹²;
- i) -CH₂OR⁴⁴, wherein R⁴⁴ is substituted lower alkyl;

and the other of R¹ or R² is selected from the group consisting of

- j) hydrogen, lower alkyl, halogen, acyl, nitro, NR¹⁴R¹⁵ (wherein R¹⁴ or R¹⁵ is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);
- k) -CH(SR³⁴)₂, wherein R³⁴ is lower alkyl or alkylene;
- l) -CH₂R³⁵, wherein R³⁵ is OR³⁶ (wherein R³⁶ is tri-lower alkyl silyl in which the three lower alkyl groups are the same or different, or is the same as R²⁹), or SR³⁷ (wherein R³⁷ is the same as R²⁷);
- m) -CO(CH₂)_qR¹⁶, wherein q is 1 to 6, and R¹⁶ is the same as R⁴;
- n) -CH(OH)(CH₂)_eR³⁸, wherein e is 1 to 6, and R³⁸ is the same as R^{4A};
- o) -(CH₂)_fCHR³⁹CO₂R⁴⁰, wherein f is 0 to 5, R³⁹ is the same as R³¹ and R⁴⁰ is the same as R³²;
- p) -(CH₂)_rR¹⁷, wherein r is 2 to 6, and R¹⁷ is the same as R⁷;
- q) -CH=CH(CH₂)_tR¹⁸, wherein t is 0 to 4, and R¹⁸ is the same as R¹²;
- r) -CH=C(CO₂R^{33B})₂, wherein R^{33B} is the same as R³³;
- s) -C≡C(CH₂)_uR¹⁹, wherein u is 0 to 4, and R¹⁹ is the same as R¹³);

R³ is hydrogen, acyl, or lower alkyl;

X is selected from the group consisting of:

- a) hydrogen;
- b) formyl;
- c) lower alkoxy carbonyl;
- d) $-\text{CONR}^{20}\text{R}^{21}$, wherein:

R^{20} and R^{21} independently are:

hydrogen;

lower alkyl;

$-\text{CH}_2\text{R}^{22}$, wherein R^{22} is hydroxy, or

$-\text{NR}^{23}\text{R}^{24}$ (wherein R^{23} or R^{24} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, or the residue of an α -amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{23} and R^{24} are combined with a nitrogen atom to form a heterocyclic group); and

- e) $-\text{CH}=\text{N}-\text{R}^{25}$, wherein R^{25} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

Y is hydroxy, lower alkoxy, aralkyloxy, or acyloxy; or

X and Y combined represent, $-\text{X}-\text{Y}-$, $=\text{O}$, $-\text{CH}_2\text{O}(\text{C}=\text{O})\text{O}-$, $-\text{CH}_2\text{OC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{NR}^{26}\text{C}(\text{=O})-$ (wherein R^{26} is hydrogen or lower alkyl), $-\text{CH}_2\text{NHC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{OS}(\text{=O})\text{O}-$, or $-\text{CH}_2\text{OC}(\text{CH}_3)_2\text{O}-$; and

W^1 and W^2 are hydrogen, or W^1 and W^2 together represent oxygen;

or a pharmaceutically acceptable salt thereof.

13. A method for enhancing the survival of a trophic factor responsive cell, comprising the step of contacting said cell with a compound of claim 2.

14. A method for enhancing the survival of a trophic factor responsive cell, comprising the step of contacting said cell with a compound of claim 5.

15. The method of claim 12, wherein said trophic factor responsive cell is a neuron.

16. The method of claim 15, wherein said neuron is a cholinergic neuron.

wherein:

one of R_1 and R_2 is selected from the group consisting of:

a) $-\text{CO}(\text{CH}_2)_j\text{R}_4$, wherein j is 1 to 6, and R_4 is selected from the group consisting of:

1) hydrogen and a halogen;

2) $-\text{NR}_5\text{R}_6$, wherein R_5 and R_6 , independently are hydrogen, substituted lower alkyl, unsubstituted heteroaryl, unsubstituted aralkyl, lower alkylaminocarbonyl, or lower alkoxy carbonyl; or R_5 and R_6 are combined with a nitrogen atom to form a heterocyclic group;

3) N^3 ;

4) $-\text{SR}_7^2$, wherein R_7^2 is selected from the group consisting of:

i) hydrogen;

ii) substituted lower alkyl;

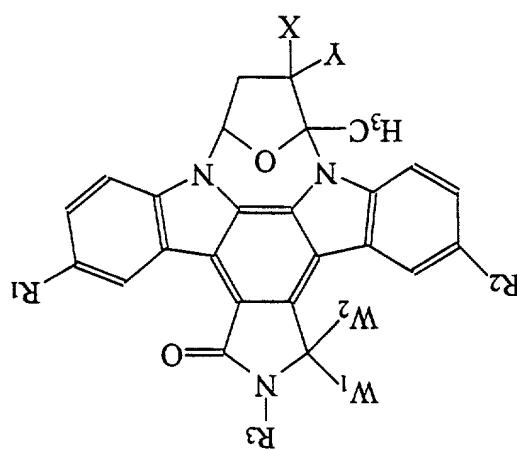
iii) unsubstituted lower alkyl;

iv) substituted aryl;

v) unsubstituted aryl;

vi) substituted heteroaryl;

vii) unsubstituted heteroaryl;



17. A method for enhancing the survival of a cell at risk of dying, comprising the step of contacting said cell with a compound defined by the general formula (I):

viii) substituted aralkyl;

ix) unsubstituted aralkyl;

x) thiazolinyl;

xi) $-(CH_2)_aCO_2R^{28}$, wherein a is 1 or 2, and R^{28} is selected from the group consisting of: hydrogen and lower alkyl; and

xii) $-(CH_2)_aCONR^5R^6$; and

5) OR^{29} (wherein R^{29} is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, or COR^{30} (wherein R^{30} is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl));

b) $-CH(OH)(CH_2)_bR^{4A}$, wherein b is 1 to 6 and R^{4A} is hydrogen or the same as R^4 ;

c) $-(CH_2)_dCHR^{31}CO_2R^{32}$ wherein d is 0 to 5, R^{31} is hydrogen, $-CONR^5R^6$, or CO_2R^{33} (wherein R^{33} is hydrogen or lower alkyl), and R^{32} is hydrogen or lower alkyl;

d) $-(CH_2)_dCHR^{31}CONR^5R^6$;

e) $-(CH_2)_kR^7$ wherein k is 2 to 6, and R^7 is halogen, CO_2R^8 (wherein R^8 is hydrogen, lower alkyl, substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl), $CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^9 (wherein R^9 is hydrogen, substituted lower alkyl, unsubstituted lower alkyl, acyl substituted aryl, or unsubstituted aryl), SR^{27B} (wherein R^{27B} is the same as R^{27}), $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are the same as R^5 and R^6) or N_3 ;

f) $-CH=CH(CH_2)_mR^{12}$ wherein m is 0 to 4, and R^{12} is hydrogen, lower alkyl, CO_2R^{8A} (wherein R^{8A} is the same as R^8), $-CONR^5R^6$, substituted aryl, unsubstituted aryl, substituted heteroaryl, unsubstituted heteroaryl, OR^{9A} (wherein R^{9A} is the same as R^9), or $NR^{10A}R^{11A}$ (wherein R^{10A} and R^{11A} are the same as R^5 and R^6);

g) $-CH=C(CO_2R^{33A})_2$, wherein R^{33A} is the same as R^{33} ;

h) $-C\equiv C(CH_2)_nR^{13}$, wherein n is 0 to 4, and R^{13} is the same as R^{12} ;

i) $-CH_2OR^{44}$, wherein R^{44} is substituted lower alkyl;

and the other of R^1 or R^2 is selected from the group consisting of

j) hydrogen, lower alkyl, halogen, acyl, nitro, $NR^{14}R^{15}$ (wherein R^{14} or R^{15} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, acyl, carbamoyl, lower alkylaminocarbonyl, substituted arylaminocarbonyl or unsubstituted arylaminocarbonyl);

- k) $-\text{CH}(\text{SR}^{34})_2$, wherein R^{34} is lower alkyl or alkylene;
- l) $-\text{CH}_2\text{R}^{35}$, wherein R^{35} is OR^{36} (wherein R^{36} is tri-lower alkyl silyl in which the three lower alkyl groups are the same or different, or is the same as R^{29}), or SR^{37} (wherein R^{37} is the same as R^{27});
- m) $-\text{CO}(\text{CH}_2)_q\text{R}^{16}$, wherein q is 1 to 6, and R^{16} is the same as R^4 ;
- n) $-\text{CH}(\text{OH})(\text{CH}_2)_e\text{R}^{38}$, wherein e is 1 to 6, and R^{38} is the same as R^{4A} ;
- o) $-(\text{CH}_2)_f\text{CHR}^{39}\text{CO}_2\text{R}^{40}$, wherein f is 0 to 5, R^{39} is the same as R^{31} and R^{40} is the same as R^{32} ;
- p) $-(\text{CH}_2)_r\text{R}^{17}$, wherein r is 2 to 6, and R^{17} is the same as R^7 ;
- q) $-\text{CH}=\text{CH}(\text{CH}_2)_t\text{R}^{18}$, wherein t is 0 to 4, and R^{18} is the same as R^{12} ;
- r) $-\text{CH}=\text{C}(\text{CO}_2\text{R}^{33B})_2$, wherein R^{33B} is the same as R^{33} ;
- s) $-\text{C}\equiv\text{C}(\text{CH}_2)_u\text{R}^{19}$, wherein u is 0 to 4, and R^{19} is the same as R^{13});

R^3 is hydrogen, acyl, or lower alkyl;

X is selected from the group consisting of:

- a) hydrogen;
- b) formyl;
- c) lower alkoxy carbonyl;
- d) $-\text{CONR}^{20}\text{R}^{21}$, wherein:

R^{20} and R^{21} independently are:

hydrogen;

lower alkyl;

$-\text{CH}_2\text{R}^{22}$, wherein R^{22} is hydroxy, or

$-\text{NR}^{23}\text{R}^{24}$ (wherein R^{23} or R^{24} is hydrogen or lower alkyl, and the other is hydrogen, lower alkyl, or the residue of an α -amino acid in which the hydroxy group of the carboxyl group is excluded, or R^{23} and R^{24} are combined with a nitrogen atom to form a heterocyclic group); and

- e) $-\text{CH}=\text{N}-\text{R}^{25}$, wherein R^{25} is hydroxy, lower alkoxy, amino, guanidino, or imidazolylamino;

Y is hydroxy, lower alkoxy, aralkyloxy, or acyloxy; or

X and Y combined represent, $-\text{X}-\text{Y}-$, $=\text{O}$, $-\text{CH}_2\text{O}(\text{C}=\text{O})\text{O}-$, $-\text{CH}_2\text{OC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{NR}^{26}\text{C}(\text{=O})-$ (wherein R^{26} is hydrogen or lower alkyl), $-\text{CH}_2\text{NHC}(\text{=S})\text{O}-$, $-\text{CH}_2\text{OS}(\text{=O})\text{O}-$, or $-\text{CH}_2\text{OC}(\text{CH}_3)_2\text{O}-$; and

W^1 and W^2 are hydrogen, or W^1 and W^2 together represent oxygen; or a pharmaceutically acceptable salt thereof.

18. A method for enhancing the survival of a cell at risk of dying, comprising the step of contacting said cell with a compound of claim 2.

19. A method for enhancing the survival of a cell at risk of dying, comprising the step of contacting said cell with a compound of claim 5.

20. The method of claim 17, wherein said cell is at risk of dying due to a process selected from the group consisting of aging, trauma, and disease.

21. The method of claim 20, wherein said cell is a neuron.

22. The method of claim 16, wherein said method is used in the treatment of Huntington's disease.

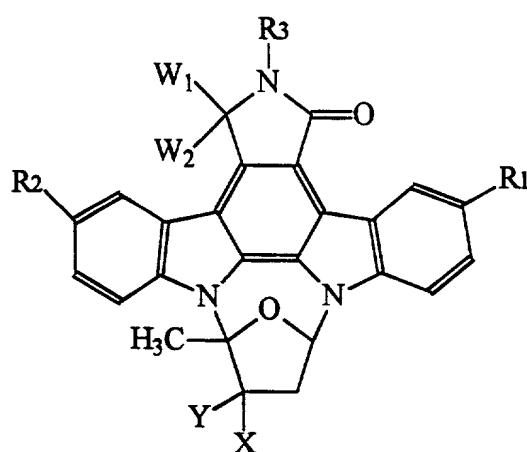
SELECTED DERIVATIVES OF K-252A

ABSTRACT OF THE DISCLOSURE

5

Disclosed herein are selected indolocarbazole derivatives which are represented by the general formula:

10



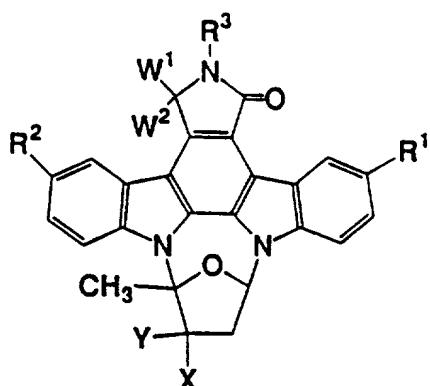
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The compounds are useful for enhancing the function and/or survival of a trophic factor responsive cell. They inhibit interleukin-2 production and have immunosuppressive activity.

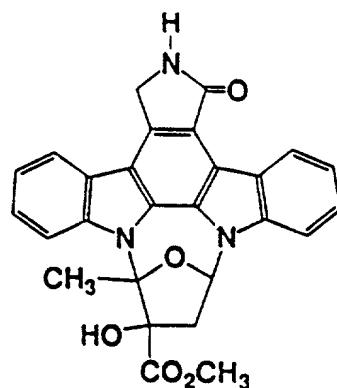
[Fig.1,3]

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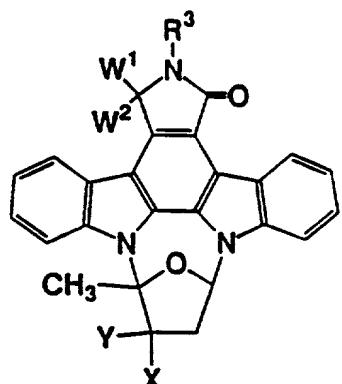
(I)

[Fig.2]



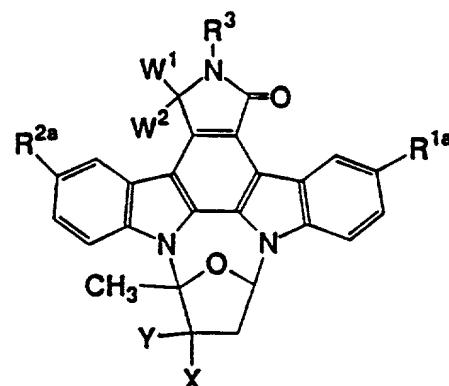
K-252a

[Fig.4]



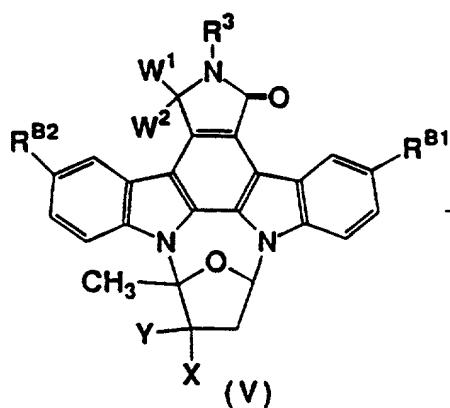
(II)

Step 1-1
Step 1-2

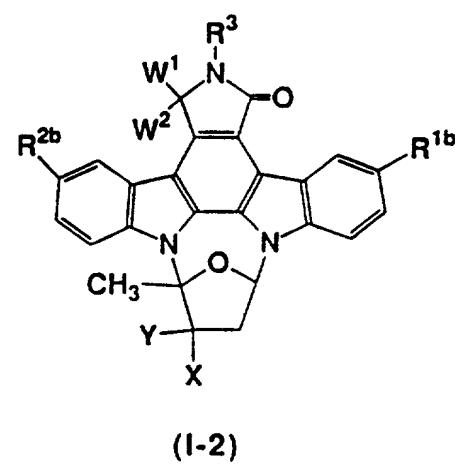


(I-1)

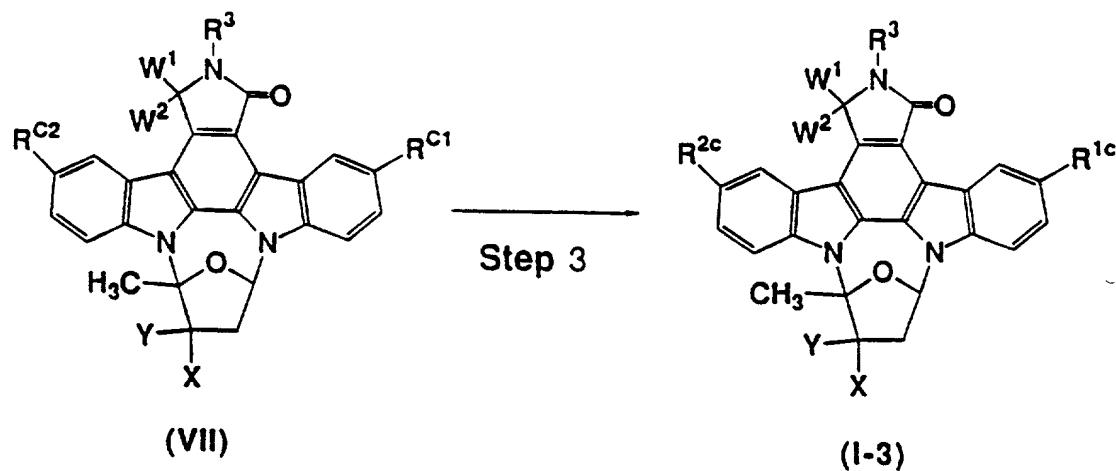
[Fig.5]



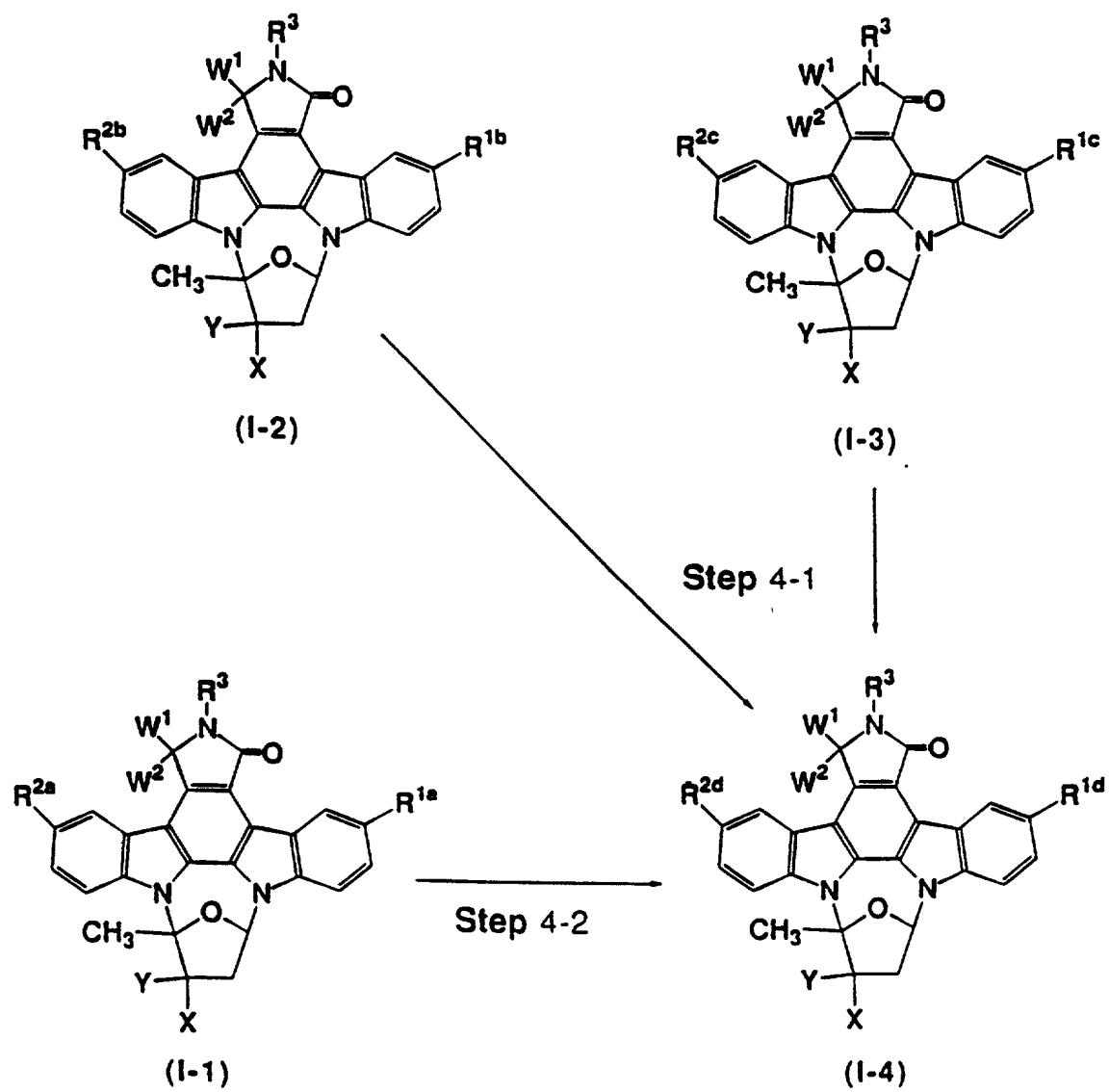
Step 2-1
~2-5



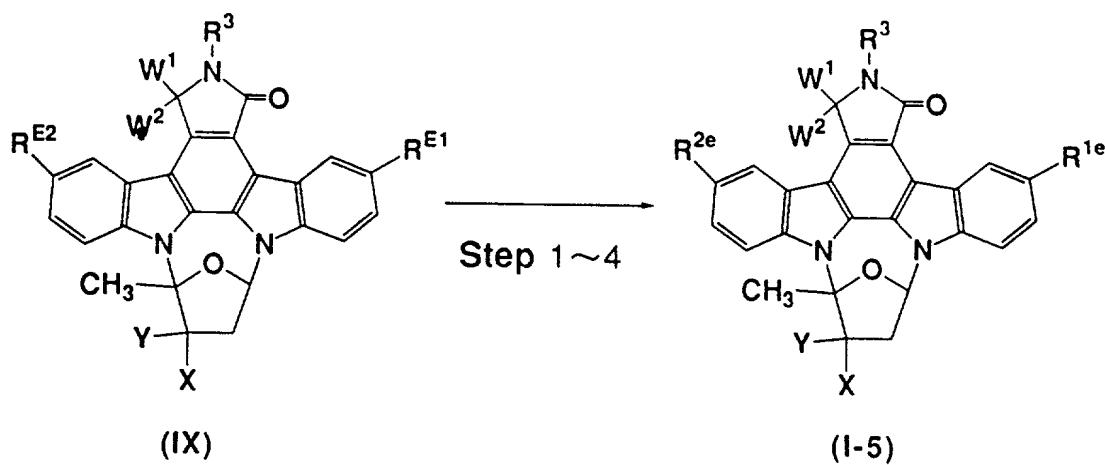
[Fig.6]



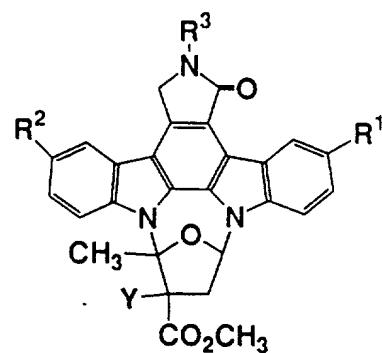
[Fig.7]



(Fig.8)



[Fig.9]



Compound	R ¹	R ²	R ³	Y
a	CHO	CHO	Ac	OAc
b	CHO	H	Ac	OAc
c	H	H	Ac	OAc
d	Ac	H	Ac	OAc
e	CH ₂ OH	H	Ac	OAc
f	CH ₂ OH	CH ₂ OH	Ac	OAc
g	Ac	Ac	Ac	OAc
h	CH ₂ OH	CH ₂ OH	H	OH

DOCKET NO.: CEPH-0512

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Robert L. Hudkins, John P. Mallamo, Masami Hamano, Rieko Tanaka, and Chikara Murakata

Serial No.: 08/867,084

Examiner: J. Parkin

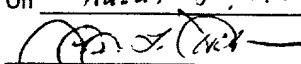
Filing Date: June 2, 1997

Group Art Unit: 1648

For: SELECTED DERIVATIVES OF K-252A

I, **Gregory L. Hillyer**, Registration No. 44,154 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

On August - 30, 1997



Gregory L. Hillyer Reg. No. 44,154

BOX DSD
Commissioner of Patents & Trademarks
Washington, DC 20231

Sir:

POWER OF ATTORNEY WITH REVOCATION
AND CERTIFICATE UNDER 37 CFR 3.73(b)

Revoking any and all powers of attorney heretofore given in the matter of the above-entitled patent application, the undersigned, assignee of the entire interest in the above-identified patent application, hereby appoints the attorneys listed below of the firm of WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS, LLP, One Liberty Place - 46th Floor, Philadelphia, Pennsylvania, 19103, as attorneys for applicant, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments

therein, to receive the patent, and to transact all business in the Patent and Trademark Office connected therewith.

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Richard E. Kurtz	Registration No. 19,263
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Mitchell R. Brustein	Registration No. 38,394
Thomas E. Watson	Registration No. 43,243
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Philadelphia, PA 19103
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CERTIFICATE UNDER 37 C.F.R. §3.73(b)

Kyowa Hakko Kogyo Co., a Japanese corporation, certifies that it is the assignee of the entire right, title and interest in and to certain inventions described and claimed in the above-identified patent application/patent by virtue of:

An Assignment from Masami Hamano, Rieko Tanaka and Chikara Murakata, three of the inventors of the patent application/patent identified above. This

assignment was recorded in the Patent and Trademark Office on November 10, 1997 at Reel 8791, Frames 0178-79. (A copy of the assignment, as executed and recorded, is attached hereto.)

The undersigned has reviewed all the documents in the chain of title of the patent application/patent identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee, **Kyowa Hakko Kogyo Co., Ltd.**

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.


Signature
Name: Seiga Itoh
Corporation: Kyowa Hakko Kogyo Co., Ltd.
Title: Director

Date: July 27, 1999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**In Re Application of:**

Hudkins et al.

Serial No.: N/A**Group Art Unit:** N/A**Filed:** Herewith**Examiner:** N/A**For: SELECTED DERIVATIVES OF K-252a**

Assistant Commissioner for Patents
Washington DC 20231

Sir:

ASSOCIATE POWER OF ATTORNEY

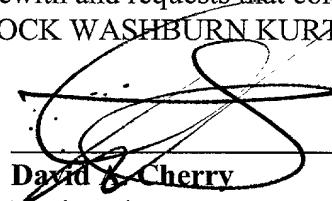
The undersigned, of the firm WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP, One Liberty Place - 46th Floor, Philadelphia, Pennsylvania
19103, Attorney and/or Agents for Applicant(s), hereby appoints the following:

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Richard E. Kurtz	Registration No. 19,263	Harold H. Fullmer	Registration No. 42,560
John J. Mackiewicz	Registration No. 19,709	William R. Richter	Registration No. 43,879
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his/her associates with full power to prosecute the above-identified application and to transact all business in the Patent Office connected therewith and requests that correspondence continue to be directed to the firm of WOODCOCK WASHBURN KURTZ MACKIEWICZ & NORRIS LLP at the above address.

Date: *11/8/00*



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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled SELECTED DERIVATIVES OF K-252A, the specification of which is attached hereto.

was filed on _____ as Application Serial No. _____
and was amended on _____.

was described and claimed in PCT International Application No. _____
filed on _____ and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. SERIAL NO.	FILING DATE	STATUS
<u>08/657,366</u>	<u>June 3, 1996</u>	<input checked="" type="checkbox"/> Pending <input type="checkbox"/> Issued <input type="checkbox"/> Abandoned

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Gary L. Creason, Reg. No. 34,310; Janis K. Fraser, Reg. No. 34,819; Richard P. Burgoon, Jr., Reg. No. 34,787; George N. Sausen, Reg. No. 26,922; William E. Booth, Reg. No. 28,933; John W. Freeman, Reg. No. 29,066; Timothy A. French, Reg. No. 30,175; Alan H. Gordon, Reg. No. 26,168; John F. Land, Reg. No. 29,554; John B. Pegram, Reg. No. 25,198; Rene D. Tegtmeier, Reg. No. 33,567; Hans R. Troesch, Reg. No. 36,950; Dorothy P. Whelan, Reg. No. 33,814; Charles C. Winchester, Reg. No. 21,040.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

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